tures, treatment assignment, and procedural variables, and the results are expressed as odds ratios with 95 percent confidence intervals. The statistical-analysis plan prespecified that the primary intention-to-treat population would consist of all patients in whom an attempt was made to implant a study stent. All P values are two-sided.

[redacted]

ENROLLMENT AND BASE-LINE CHARACTERISTICS

Between March 29 and July 8, 2002, 1326 patients at 73 U.S. centers were assigned to receive either a paclitaxel-eluting stent (667 patients) or a bare-metal stent (659 patients). Twelve patients (0.9 percent) were subsequently excluded because the appropriate stent size was not available for three patients, the guide wire or pre-dilation balloon could not be successfully passed in three, complications occurred before stenting in three, the lesion was reevaluated before stenting and determined to meet exclusion criteria in two, and withdrawal of consent by one. The population included in the analysis therefore consisted of 1314 patients: 662 were assigned to receive paclitaxel-eluting stents, and 652 to receive the bare-metal stents. The base-line characteristics of the two groups were well matched (Table 1).

PROCEDURAL OUTCOMES

The number of stents implanted per patient, the mean length and diameter of the stents, and other deployment and implantation variables were similar in the two groups (Table 2). The initial angiographic results were also similar in the two cohorts.

CLINICAL OUTCOMES

As shown in Table 3, implantation of the paclitaxel-eluting stent, as compared with the bare-metal stent,

[redacted]

* CI denotes confidence interval.

† Patients undergoing both percutaneous coronary intervention and coronary-artery bypass grafting during follow-up are counted as having a single target-vessel revascularization event.

‡ Major adverse cardiac events were death from cardiac causes, myocardial infarction, or ischemia-driven target-vessel revascularization.

§ Target-vessel failure was defined by death, myocardial infarction, or ischemia-driven revascularization related to the target vessel.

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* Plus–minus values are means ±SD. The analysis included 559 patients who underwent follow-up angiography at nine months as prespecified in the protocol. CI denotes confidence interval.
† Loss index was determined by dividing late loss by acute gain.
‡ Binary restenosis was defined as stenosis of at least 50 percent of the luminal diameter of the treated lesion.
§ The pattern of restenosis was defined according to the classification of Mehran et al.[25]
¶ Data were not available for one patient who received a paclitaxel-eluting stent.

reduced the primary end point of the risk of target-vessel revascularization at nine months by 61 percent and lowered the risk of target-lesion revascularization by 73 percent, a consequence of significant reductions in the rates of both percutaneous coronary intervention and coronary-artery bypass grafting. Multivariate analysis showed that randomization to the group receiving a paclitaxel-eluting stent was an independent predictor of freedom from target-vessel revascularization (odds ratio, 0.34; 95 percent confidence interval, 0.22 to 0.54; P<0.001). The rates of death, myocardial infarction, and stent thrombosis were low and similar in the two groups. Thus, at the end of the nine-month follow-up period, the rates of target-vessel failure and major adverse cardiac events were significantly lower after the receipt of a paclitaxel-eluting stent than after the receipt of a bare-metal stent (Table 3).

ANGIOGRAPHIC RESULTS

Follow-up angiography at nine months was completed in 559 of the 732 prespecified patients (76.4 percent), including 442 of the 536 patients (82.5 percent) from the original prespecified angiographic cohort and 117 of the 196 patients (59.7 percent) from the extended long-lesion cohort, from whom consent for angiographic follow-up had not initially been obtained. There were no significant base-line clinical or angiographic differences between patients in whom follow-up angiography was sched-

uled and those in whom it was not scheduled, except that the lesion was significantly longer in patients in the follow-up angiographic cohort (mean, 14.4±6.9 vs. 12.1±5.1 mm; P<0.001). Among patients in the angiographic follow-up cohort, diabetes mellitus was present in 27.7 percent of those who received a paclitaxel-eluting stent and 23.8 percent of those who received a bare-metal stent (P=0.24), and the mean lesion length was 14.4±6.7 and 14.4±7.1 mm, respectively (P=0.94).

Quantitative follow-up data were available for 559 patients. As compared with those who received a bare-metal stent, patients who received a paclitaxel-eluting stent had a significantly smaller amount of late loss and a lower loss index, resulting in greater luminal dimensions and a smaller degree of stenosis at follow-up, both within the stented segment and at its edges (Table 4 and Fig. 1). The use of a paclitaxel-eluting stent reduced the risk of binary restenosis by 77 percent within the stent and by 70 percent in the analysis segment.

Multivariate analysis showed that randomization to the group that received a paclitaxel-eluting stent was an independent predictor of freedom from restenosis (odds ratio, 0.16; 95 percent confidence interval, 0.08 to 0.30; P<0.001).

The relative reduction in the risk of restenosis with the paclitaxel-eluting stent, as compared with the bare-metal stent, was independent of diabetes mellitus status, epicardial-vessel location, and the length and diameter of the lesion or stent (Fig. 2). Among patients with restenosis, those treated with the paclitaxel-eluting stent were much less likely than those who received a bare-metal stent to have a diffuse or proliferative pattern of hyperplasia, and they had a significantly shorter restenosed segment (Table 4). Aneurysms were present at nine months in two patients (0.7 percent) in each group; only one of these aneurysms (in a patient who received a bare-metal stent) developed during the nine-month follow-up period.

Among patients in the angiographic cohort who completed follow-up angiography, the rate of target-lesion revascularization was reduced from 14.6 percent with the bare-metal stent to 3.8 percent with the paclitaxel-eluting stent (P<0.001). Among patients who did not undergo angiographic follow-up, the rate of target-lesion revascularization was reduced from 9.2 percent with the bare-metal stent to 2.4 percent with the paclitaxel-eluting stent (P<0.001).

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In this prospective, randomized, double-blind study, the implantation of a slow-release, polymer-based, paclitaxel-eluting stent markedly reduced the risk of clinical and angiographic restenosis as compared with the implantation of a bare-metal stent, in patients with a wide range of previously untreated coronary lesions. Despite the relatively low rate of restenosis in the control group, the biologic potency of the paclitaxel-eluting stent was evidenced by a 70 percent relative reduction in the risk of angiographic restenosis, with a corresponding 73 percent reduction in the risk of target-lesion revascularization. In addition to reducing the need for repeated percutaneous coronary intervention, the paclitaxel-eluting stent also reduced the need for coronary-artery bypass grafting. Notably, target-lesion revascularization was required in only 3.8 percent of patients assigned to receive a paclitaxel-eluting stent who underwent protocol-specified angiographic follow-up, and the rate was also significantly reduced among patients who received a paclitaxel-eluting stent who did not undergo routine angiographic follow-up.

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The paclitaxel-eluting stent effectively reduced the risk of restenosis in a broad range of lesions and patients undergoing percutaneous intervention. The three principal determinants of restenosis after coronary-stent implantation are diabetes mellitus status, the reference-vessel diameter, and the lesion length (or the length of the implanted stent).[26-30] We found that the risk of restenosis was increased by approximately 50 percent among diabetic patients who received a bare-metal stent as compared with those without diabetes who received such a stent. In contrast, the risk of restenosis was reduced by more than 80 percent among patients with diabetes who received a paclitaxel-eluting stent, so that these patients and patients without diabetes had similar rates of angiographic recurrence after the receipt of such a stent. The marked efficacy of site-specific paclitaxel delivery in reducing the risk of restenosis among patients with diabetes may be explained by paclitaxel's ability to disrupt microtubules, leading to inhibition of signal-transduction pathways regulated by insulin that mediate growth, differentiation, and stress responses.[31] The rates of restenosis after the implantation of a bare-metal stent in small coronary arteries (no more than 2.5 mm in diameter) and long lesions (longer than

20 mm) were also increased, by 38.5 percent and 41.5 percent, respectively. The benefits of the paclitaxel-eluting stent were particularly evident in these subtypes of lesions, which had the greatest absolute reductions in the risk of restenosis.

The ability of the paclitaxel-eluting stent to reduce the extent of neointimal hyperplasia was evident both within the stent and at the proximal and distal margins of the stent. Moreover, when restenosis did occur after the implantation of a paclitaxel-eluting stent, the pattern was much more likely to be focal than diffuse or proliferative, potentially translating into easier subsequent management.[25]

Use of the paclitaxel-eluting stent was safe, with no excess risks apparent. Stent thrombosis was infrequent in both groups, and no late stent thromboses occurred after clopidogrel was discontinued at six months. The rates of death from cardiac causes and myocardial infarction over the nine-month follow-up period were also low and were not significantly different between the two groups. Aneurysms did not develop during the nine-month follow-up period in any patient who received a paclitaxel-eluting stent.

The safety and efficacy of the slow-release, polymer-based, paclitaxel-eluting stent in our study population cannot be generalized to patients and types of lesions that were excluded from randomization, including lesions resulting from acute myocardial infarction, thrombus-containing lesions, bifurcations, stenoses of the left main coronary artery, heavily calcified stenoses, vessels visually estimated as less than 2.5 mm or greater than 3.75 mm in diameter, diseased saphenous-vein grafts, or lesions with in-stent restenosis. The extent to which an injured or unstented margin contributed to the remaining cases of focal restenosis with the paclitaxel-eluting stent cannot be determined with certainty. Moreover, overlapping stents were implanted in relatively few patients in this trial, and thus, further study is required to evaluate the treatment of lesions that are longer than 28 mm, which require at least two stents. Extended follow-up is required to establish the long-term safety of this and other drug-eluting stent devices. All of our patients received clopidogrel for six months in order to maximize the safety of this device (though preclinical studies demonstrated equivalent rates of healing with the use of nonoverlapping bare-metal stents and slow-release, paclitaxel-eluting stents). Though the use of a prolonged course of clopidogrel is consistent with current studies demonstrating an incremental benefit of extended thienopyridine therapy,[32] it is unknown whether this duration of treatment is necessary to prevent subacute thrombosis after the implantation of a paclitaxel-eluting stent. Finally, appropriately powered, head-to-head, randomized trials comparing different drug-eluting stent systems are required to evaluate their relative safety and efficacy.

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Drs. Stone, Ellis, Hermiller, and Caputo report having served as consultants or advisors to Boston Scientific; Dr. Stone transiently held an equity interest in Boston Scientific, which was liquidated before the study results became available; Dr. Greenberg reports holding an equity interest in Boston Scientific; Drs. Stone, Hermiller, Caputo, and Popma report having received lecture fees from the sponsor; Dr. Russell reports serving as a full-time employee of the sponsor and holding equity.

APPENDIX

Members of the TAXUS-IV Study were as follows: *Executive Committee* — G. Stone (principal investigator), Cardiovascular Research Foundation and Lenox Hill Heart and Vascular Institute, New York; S. Ellis (co-principal investigator), Cleveland Clinic Foundation, Cleveland; P. Teirstein, Scripps Clinic, La Jolla, Calif.; D. Cohen, Beth Israel Deaconess Medical Center, Boston; M. Russell, Boston Scientific, Natick, Mass.; *Data Monitoring* — PAREXEL International, Waltham, Mass.: R. Baldwin (coordinator), Boston Scientific; *Data Management and Biostatistical Analysis* — PAREXEL International: P. Lam (director); M. Cody (coordinator), Boston Scientific; *Clinical Events Adjudication Committee* — Harvard Cardiovascular Research Institute, Boston: D. Cutlip (chair), M. Chauhan, K. Ho, J. Aroesty, J. Kannam; *Data and Safety Monitoring Committee* — B. Gersh (chair), Mayo Clinic, Rochester, Minn.; M. Ohman, University of North Carolina, Chapel Hill, Chapel Hill; T. Ryan, Boston Medical Center, Boston; D. Faxon, University of Chicago, Chicago; D. DeMets, University of Wisconsin, Madison; *Angiographic Core Laboratory* — Brigham and Women's Hospital, Boston: J. Popma (director), J. Shah, A. Wong; *Intravascular Ultrasound Imaging Core Laboratory* — Washington Hospital Center, Washington, D.C.: N. Weissman (director); *Study Sites, Principal Investigators, and Study Coordinators* — *Huntsville Hospital, Huntsville, Ala.*: W. Strickland, D. McCrackin; *Good Samaritan Regional Medical Center, Phoenix, Ariz.*: N. Laufer, D. Cook; *Scripps Memorial Hospital, La Jolla, Calif.*: M. Buchbinder, S. Costello; *Mercy General Hospital, Sacramento, Calif.*: M. Chang, S. Bordash; *University of California Davis Medical Center, Sacramento*: R. Low, K. Harder; *Good Samaritan Hospital, Los Angeles*: R. Matthews, S. Mullin; *Scripps Clinic, La Jolla, Calif.*: P. Teirstein, E. Anderson; *Stanford Medical Center, Stanford, Calif.*: A. Yeung, P. Tsao; *Columbia Medical Center of Aurora, Aurora, Colo.*: B. Molk, K. Bickett; *Aurora Denver Cardiology, Denver*: B. Molk, K. Bickett; *Connecticut Clinical Research, Bridgeport*: E. Kosinski, M. Capasso; *Washington Hospital Center, Washington, D.C.*: L. Satler, R. Howery; *Christiana Hospital, Newark, Del.*: J. Hopkins, K. Sullivan; *Sarasota Memorial Hospital, Sarasota, Fla.*: S. Culp, J. Selby; *MediQuest Research Group, Ocala, Fla.*: R. Feldman, K. Tighe; *Florida Hospital, Orlando*: J. Greenberg, M. Allan; *St. Vincent's Hospital, Jacksonville, Fla.*: G. Pilcher, A. Dennis; *Piedmont Hospital, Atlanta*: C. Brown, A. Garvitte; *Mercy Hospital Medical Center, Des Moines, Iowa*: M. Tannenbaum, R. Porter; *Mercy Medical Center, Des Moines, Iowa*: M. Tannenbaum, M. Craig; *Northwestern University Medical School, Chicago*: C. Davidson, L. Goodreau; *St. John's Hospital, Springfield, Ill.*: G. Mishkel, P. Warren; *Community Hospital Heart Institution, India-*

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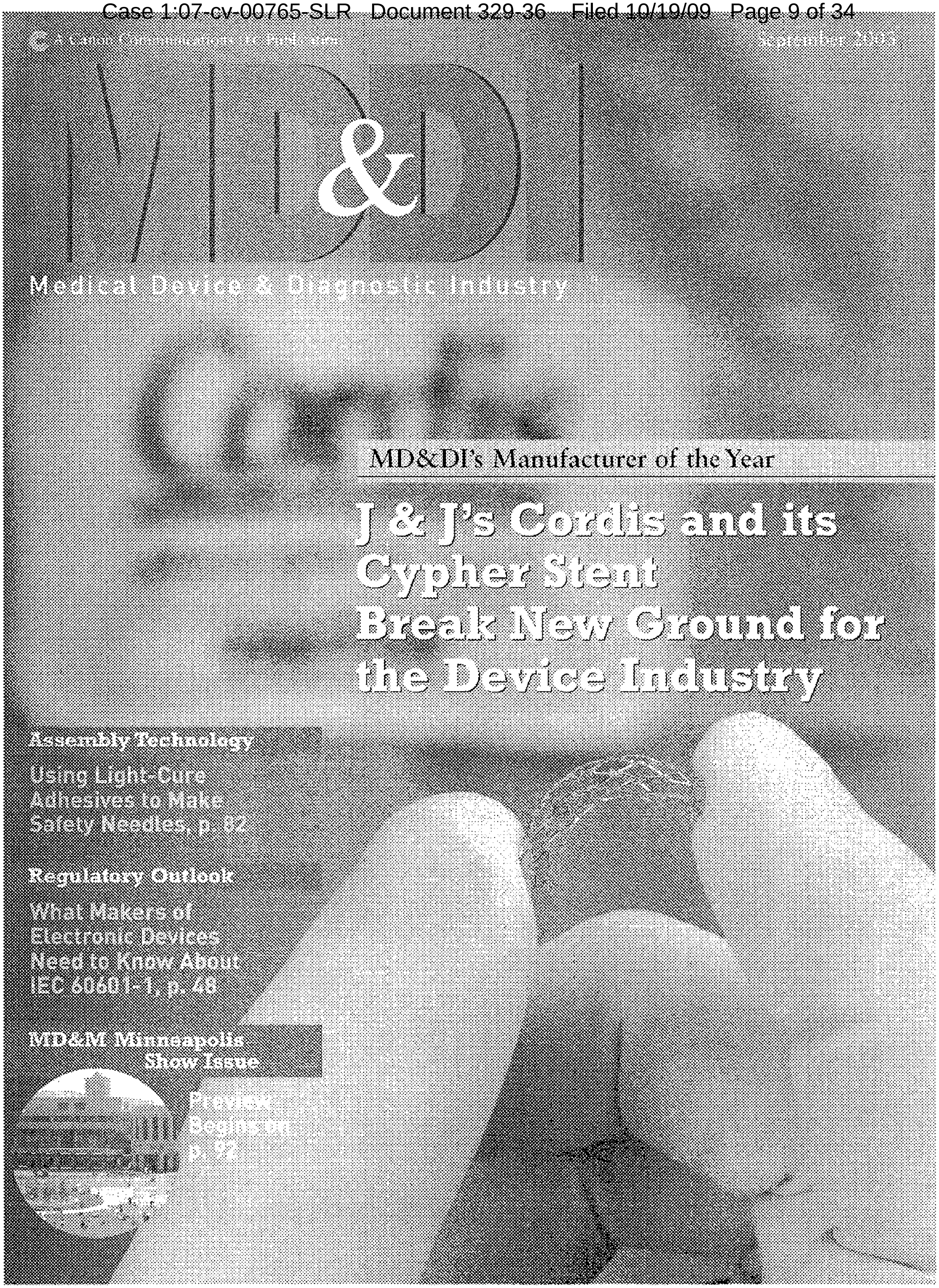
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J & J's Cordis and its Cypher Stent Break New Ground for the Device Industry
Assembly Technology
Using Light-Cure Adhesives to Make Safety Needles, p. 82
Regulatory Outlook
What Makers of Electronic Devices Need to Know About IEC 60601-1, p. 48
MD&M Minneapolis Show Issue
Preview: Begins on p. 92

Blazing New Paths for Product Introductions

In getting its Cypher stent to market, Johnson & Johnson's Cordis subsidiary not only assumed leadership of the emerging combination product market, but also broke new ground in coordinated FDA-CMS approvals.

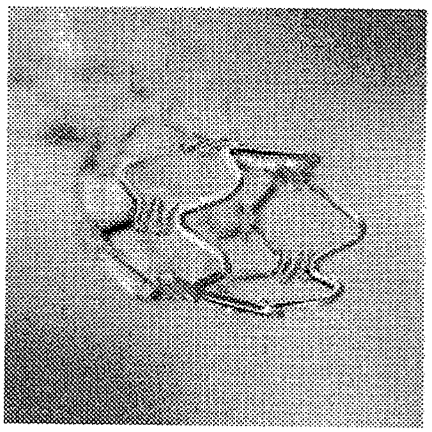
Erik Swain

A technology that leads to significantly improved patient outcomes compared with existing treatments. A touchstone for the convergence of two industries. An unprecedented success in attaining Medicare coverage. What do these add up to? A potential revolution.

The Cypher sirolimus-eluting coronary stent, manufactured by Cordis Corp. (Miami Lakes, FL), a Johnson & Johnson (New Brunswick, NJ) company, is not only a leap forward in the treatment of cardiovascular disease; it could change the way the device industry pursues approval and reimbursement for combination products. The Cypher stent also was the first product to have Medicare reimbursement coverage in place before receiving FDA approval. For these and other reasons, the company has earned the distinction of being named *MD&DI*'s Medical Manufacturer of the Year.

The company is not being cited for the success of this product alone. It is also being acknowledged because of the expertise and resources it could muster in the design, development, and manufacturing of this and other products. These qualities combine to produce the excellence that characterizes the device industry at its best.

Erik Swain is the East Coast editor for MD&DI *and contributes frequently to the magazine.*



The Cypher Sirolimus-Eluting coronary stent, manufactured by Cordis, represents a significant leap forward in combination products.

FDA's approval of Cypher on April 24, 2003, was the first marketing approval for a drug-eluting stent in the United States. And drug-eluting stents so far represent the pinnacle of the combination product field, which harnesses the strengths of the device industry and those of the drug or biologics industries to produce technologies that could not be developed by either sector alone.

"This is a very exciting time for Cordis and the device industry in general, because [the Cypher] is opening the door to the future of the industry—the area of combination products," says Michael Drues, PhD, president, Vascular Sciences (North Grafton, MA). "Many device firms take an overly simplistic view of cardiovascular disease. Partly as a result of this [technology], some of them are starting to change their thinking."

The impact in this case is that the incidence of restenosis, or reblockage of the artery, has been reduced significantly, and almost eliminated among low-risk patients. This breakthrough in cardiovascular care has been the talk of the device industry in 2003.

"Rarely are there instances where a new medical technology and/or surgical procedure is introduced that has such a dramatic improvement on the outcome of that type of procedure," says Patrick Driscoll, president, MedMarket Diligence (Foothill Ranch, CA).

The company had to address a number of drug-related manufacturing challenges, such as maintaining stability and purity as well as controlling a precise rate of release once the stent is in place.

J&J's structure, philosophy, and practices enabled it to take advantage of advanced technologies, research methods, regulatory approaches, and manufacturing techniques. Here is the story of how the company's commitment to excellence may help take an entire segment of the industry in a new direction.

Product Development

The road that led to success in 2003 first began in August 1994, when FDA approved Cordis' bare-metal Palmaz-Schatz stent. It was quickly apparent that stenting solved several problems that angioplasty alone could not. But one challenge, restenosis caused by tissue proliferation, remained unmet.

By 1995, J&J began to explore how to address that problem and turned its attention to drug-based solutions, which reflected an organizational strength. J&J consists of more than 100 individual companies, and has a knowledge base that stretches as deeply into the pharmaceutical industry as it does into the device industry.

The questions, then, became what drug to use and how to apply it. By late 1995, it became clear that oral and catheter-based delivery solutions were not going to achieve the desired effectiveness, but localized, time-release delivery of a product via a stent might. And so began a significant collaboration between Cordis and many of J&J's pharmaceutical experts.

"We knew we wanted a drug that would inhibit proliferation and multiplication of cells into the vessel lumen," recalls Brian Firth, MD, PhD, vice president for medical affairs and health economics at Cordis. "It had to be highly efficient in microgram quantities because there is a small amount of surface area on a stent. And it had to be nontoxic to the vessel walls. So we looked for cytostatic properties that would block cells from multiplying rather than kill them." This differed from competitors' efforts, many of which focused on cytotoxic products.

J&J also made a crucial decision early on to focus efforts on drugs already approved or on track for FDA approval, to make any future combination product application simpler. The corporation's pharmaceutical experts screened more than 800 compounds, settling on a handful to test in animals. From those efforts, sirolimus, a drug developed to prevent rejection of kidney transplants, emerged as the clear choice for testing on humans. Among the points in its favor were the fact that it did not cause cell death nor inhibit endothelial growth, which could raise the risk of thrombosis.

Identifying a potentially winning compound was impressive. But J&J matched that feat by quickly obtaining an exclusive licensing agreement with the maker of sirolimus, Wyeth Pharmaceuticals (Collegeville, PA). Again, J&J's pharmaceutical industry expertise paid off, as the corporation could draw on personnel who knew how to negotiate such an agreement.

At the same time, development proceeded on the device side. The choice to use the already-FDA-approved Bx Velocity stent, whose vessel wall uniformity and uniformity of

expansion were well suited to drug delivery, was not a tough one. The bigger challenge was finding a polymer to provide controlled release of the drug without causing irritation or inflammation in the body. Cordis approached SurModics Inc. (Eden Prairie, MN), a company with a long history of developing and producing coatings for the medical device and combination product industries.

"The biocompatibility of the coating that we identified was well established," says Jane Nichols, vice president of marketing for SurModics. "The part that took time was testing the combination of drug and coating, and making sure it was meeting the requirements of the elution profile. We had to make sure [the coating] did not interfere with the drug during the manufacturing process. J&J did a good job of looking at available coating technologies, and they understood analytical method development and drug release. We offered extensive experience [with coatings] interfacing between the body and a device."


Brian Firth, vice president for medical affairs and health economics at Cordis.

Manufacturing the finished product presented considerable challenges because drug-related issues, such as maintaining stability and purity and tightly controlling the rate of release, as well as device-related issues, such as ensuring proper sterilization procedures and proper coating application, all had to be heeded. "This caused [Cordis] to go to other manufacturing sites and use expertise from the drug side at J&J," Firth says. "That's one of the benefits of being part of J&J. You don't normally have those kinds of top-line experts in drug manufacturing at a medical device manufacturer. It was a great help to be assisted by experts outside of Cordis."

By December 1999, a little more than four years after drug-eluting stent research began in earnest, the drug, device, and coating had been chosen, and the product was ready to be tested in humans. "That's an extremely short time given that it was a new concept," Firth says.

Clinical Trials

In the world of combination products, the manufacturer is never sure whether a product might be a winner until the first clinical trials in humans are completed. Often it can take a long time to determine the product's effects. What was remarkable about Cypher's trials was how quickly it became apparent that this was a breakthrough treatment, and how well the results sustained themselves over multiple years.

The patient implants, performed in Brazil in December 1999, were part of a study investigating whether the product had any safety issues. But after four months, to everyone's amazement, "the stents looked as if they had been put in the day before," Firth says. Results for those initial 30 patients have remained excellent, with 93.3% event-free survival reported after three years. "The big question was, while they looked good at four months, would they hold up long term?" says Firth. "At three years there was hardly any change from four months." The drug was, in fact, preventing cells from dividing without destroying them, and the delivery system was, in fact, distributing the drug at the proper rate to the correct localized area.

Initial outstanding results led to the first formal clinical trial, RAVEL, conducted with 238 patients in Europe and Latin America beginning in August of 2000. Six-month results, first announced at the European Society of Cardiology meeting in September 2001, were even more stunning. "It showed zero restenosis, zero thrombosis, and zero life loss," Firth recalls. "That compares to a 26% angiographic restenosis rate for bare-metal stents. Nobody had ever seen results like this." After two years, this group still reported no thrombosis and only three of the 238 patients needed any sort of reintervention.

"RAVEL was the first multicenter trial to show no restenosis at all," says Mario Costa, MD, PhD, an interventional cardiologist who is an assistant professor of medicine and director of research at Shands Jacksonville, a University of Florida hospital. Costa has been involved in four Cypher studies. "But what is really impressive is the longevity of the results. These are not just acute results; they are there beyond the first year."

It was then time for the biggest challenge, a U.S. clinical trial with more patients and more difficult cases of cardiovascular disease. Many of the 1058 patients in this trial, called SIRIUS, had diabetes, and most had larger lesions than the RAVEL patients had had. After one year, 20% of bare-metal patients needed a repeat intervention, compared with 4.9% of Cypher patients.

"Given the preliminary data that had already come in from the European trial, I was not especially surprised by the efficacy results, but the safety results exceeded expectations," says Jeffrey W. Moses, MD, a coprincipal investigator of the SIRIUS trial and the chief of interventional cardiology at Lenox Hill Hospital and Cardiovascular Research Foundation (New York City). "The potential for complications like clotting or aneurysms was lower than I anticipated. There was no tax that you paid for the extraordinary net benefit in terms of restenosis."

Also exceptional, Moses says, was the way in which J&J conducted the data handling. "Not only did we have full access to the data, but it was ours to interpret and further analyze," he says. "They let us run with the ball. It's fairly unique in that industry to have that kind of confidence in the science. I respect them a lot for that."

CMS Approval

While J&J left the scientific data in the hands of the doctors and scientists, its regulatory and marketing experts left nothing to chance with FDA, the Center for Medicare & Medicaid Services (CMS), and hospital organizations.

Particularly notable was the early stage at which the firm met with CMS, and the amount of data it presented to bolster its case for reimbursement beyond existing diagnosis-related groups (DRGs), or incremental reimbursement. Meetings with CMS began in September 2000, after data had come back from the initial trial in Brazil. Firth and other Cordis officials sensed that "it seemed like we were onto something pretty big."

It had taken Cordis three years and three months to get incremental reimbursement for the first bare-metal stents, which meant that for the first three years they were on the market, hospitals had to absorb the increased costs of the procedure. This time, Firth recalls, Cordis was determined that would not happen again. The firm "set out to change the paradigm, and get incremental reimbursement for Cypher as close to FDA approval as humanly possible. We were going to show CMS our data every step of the way, because we wanted unique codes." The company met with a number of large private payers during the process as well. This was the savvy thing to do, Driscoll says, because many industry breakthroughs in the past have been "blown out of the water by reimbursement issues."

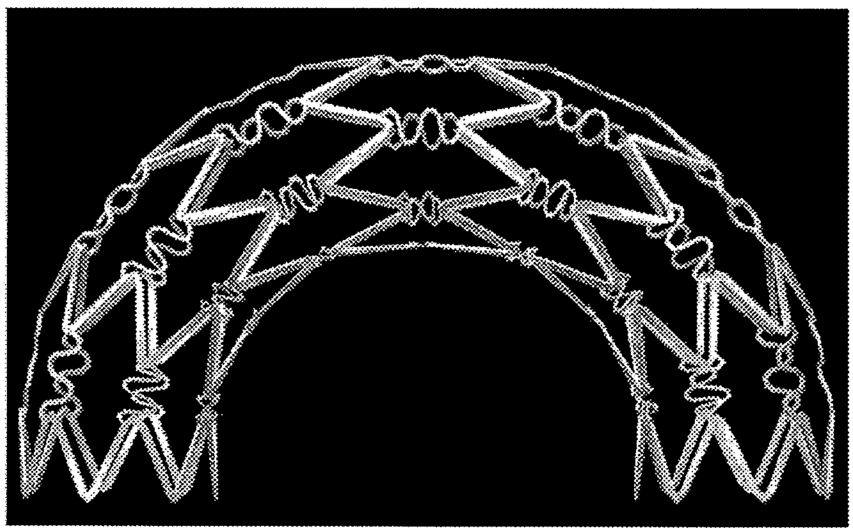
Not only was J&J quite open with CMS about all of its clinical trial results, it was also able to provide the center with a persuasive economic study. J&J sponsored a study by David J. Cohen, MD, Director of the Economic and Health Outcomes Research Group at Harvard Clinical Research Institute (Boston). The study showed that even though Cypher was going to cost $2000 more than existing stents, the average 12-month cost of using the device would be $16,813, or only $309 more than for bare-metal stents. Owing to a reduced number of reinterventions, Cypher was shown to be a virtually break-even proposition for payers.

J&J also contended that costs related to bypass surgery have decreased 5 to 10% a year over the last five to 10 years as the popularity of stents and angioplasty have grown, and that drug-eluting stents should create even further savings in that area. It also aggressively solicited support from physician groups and professional societies.

CMS took Cohen's and J&J's data, constructed its own economic models, and agreed with Cohen's conclusion. In April 2002, the center gave drug-eluting stents their own code, ICD9. In August 2002, it approved mapping the code to new DRGs (one for acute myocardial infarction applications, the second for other applications) that would pay more than those for bare-metal stents. These developments came before FDA approval, an unprecedented feat in the history of the device industry.

"I give Cordis tremendous accolades for having the foresight and the chutzpah to spend time, effort, and money up front to get reimbursement pathways in place prior to launch," says Draes. "Not only will it make it easier for physicians to get paid for using the product from the beginning, but it also might make it easier for their competitors' products to be [approved for incremental reimbursement] as well. But management had the foresight to realize how much of a benefit this would be to them."

The costs involved were not insignificant, but J&J understood why they had to be incurred. "The company seems to have conducted significant outcomes research as part of its clinical trials. That's an expensive proposition, but one that is essential to support a higher reimbursement rate," says Steve Halasey, editor of *MX* magazine (Los Angeles), a sister publication to *MD&DI* that covers financial aspects of the device industry. "Remember that J&J lost the original bare-metal stent market to competitors, mostly because its pricing was too high. It will be interesting to see if the company has learned its lesson. But other companies that have not conducted equivalent outcomes research could be at a disadvantage when it comes to justifying their pricing."



The closed-cell design of the Cypher stent platform supports uniform delivery of sirolimus. The construction is intended to reduce vessel trauma and is virtually free of recoil.

In fact, J&J's approach with Cypher may indicate a new trend in how device companies deal with reimbursement issues. "The companies most successful in being reimbursed for high-profile technologies can thoughtfully align the technical competencies in their companies with their policy and political competencies," says reimbursement expert Ted Mannen, managing director for Aventor (Washington, DC). "To be successful with a product that presents novel or complex issues, you have to have a more holistic set of skills. Increasingly, companies will make it a best practice to start reimbursement planning very early, and to include reimbursement as a discipline on the product team."

J&J and Cordis have not been content to rest on their laurels once CMS reimbursement was attained. They have engaged in a number of practices that attempt to make reimbursement easier for all involved. The company is continuing to provide CMS with data to get the DRGs adjusted upward. It also has enlisted consulting firm Ernst & Young to do a real-world economic study.

Postlaunch, Cordis has been conducting seminars to show hospitals what procedures to follow to attain proper reimbursement. It is also encouraging some hospitals to change their contracts with private payers. Those that get paid on a per diem basis (often rural hospitals) find themselves not getting reimbursed more for working with more-expensive new technology. Cordis has been encouraging such hospitals to go to a "carve-out" approach, which is based on aggregate percentages and is standard in populous or wealthy areas.

Cypher Stent Milestones

1994
The Palmaz-Schatz balloon expandable stent is approved for coronary artery applications and is cited by physicians as a "breakthrough in interventional medicine."

1996
Cordis Corp. merges with Johnson & Johnson Interventional Systems Co. to form Cordis Corp., a Johnson & Johnson company with approximately 3500 employees worldwide.

The one-millionth Palmaz-Schatz balloon-expandable stent is sold.

1997
Johnson & Johnson obtains incremental reimbursement for coronary artery stents.

2000
Cordis introduces the Bx Velocity coronary stent, which clinicians describe as a "quantum leap forward" in stent technology, combining the flexibility of a coil stent with the scaffolding of a slotted-tube stent.

Hepacoat (Carmeda end-point attached heparin) is used on the Bx Velocity coronary stent, making it the first stent with a proprietary heparin coating.

Cordis initiates enrollment in the multicenter RAVEL clinical trial of its Cypher sirolimus-eluting coronary stent to evaluate the risk of in-stent restenosis. The trial involves 238 patients at 19 sites across Europe and Latin America.

FDA Approval

The path to marketing clearance was fraught with its own challenges. The company was very confident in its clinical trial data, and it had a stent, a drug, and a coating that had been seen in FDA applications before. But it was well aware that FDA had not seen a product like Cypher before, and new product classes invite extra scrutiny.

J&J had to demonstrate a higher standard of manufacturing capability than for a regular device. It had to prove that it would manufacture to a standard of purity and quality consistent with that for drugs. It had to show that the sterilization process did not affect the drug. It had to address shelf life and stability issues that usually don't pertain to devices. It had to show that it had tight control of the quantity and rate at which the drug was coming off the device, so that the delivery process would take about 45 days as specified. It had to show that the polymer coating was compatible with the drug, remained inert in the blood vessel, and did not crack or flake off when applied to the stent. These and other factors were new challenges for a device manufacturer. But Cordis received much assistance from the experts on J&J's drug side in preparing the application and addressing the feedback from the agency.

Because the Cypher stent constituted a drug-device combination product, J&J had to work with multiple FDA centers. While CDRH took the lead in reviewing the PMA application, the Center for Drug Evaluation and Research (CDER) gave ample input, and J&J had to provide many answers to both centers. In fact, Firth says, in many respects the application received more scrutiny from CDER. "The FDA drug [center] tends to see drugs as systemic," he says. "But our product had local drug delivery, with very little spillage into the bloodstream. The drug side raised a lot of questions about the systemic effects of the drug. We had to do quite a bit of work to show that because of the local delivery, things should be viewed differently."

The application represented new territory for FDA, which has been restructuring how it handles applications and inspections for combination products. But Firth says the two centers "worked well together," and the agency completed the review in nine and a half months, which is very quick considering the complexity of the application.

So, in April 2003, Cypher became the first drug-eluting stent to gain U.S. market approval. Acceptance has been swift, and a report by JP Morgan estimates that Cypher will capture 42% of all U.S. stent sales in 2003, including 65% in the fourth quarter. That, the report states, could add up to $1.7 billion to J&J's 2003 revenues, and cause a 110% jump in revenues from the Cordis unit.

Implications for Cardiovascular Care

To maintain that kind of market presence, however, J&J will have to demonstrate that its technology is superior to other drug-eluting stents. Competition could come to the U.S. marketplace as soon as 2004.

J&J appears to have already gained a lot of goodwill with physicians. "I'm very excited about this technology," says Costa. "It's a major revolution in the way we treat coronary disease."

Firth says one thing J&J is most proud of is how the technology has improved patients' quality of life. "Patients are benefiting hugely from a device that reduces the need for repeat interventions," he says. "It is not only making the actual surgery easier, and the clinical benefit better, but it is reducing the anxiety for patients and their families that goes with surgery. It is changing what patients are going to expect."

From a more bottom-line standpoint, Driscoll says, the product has "changed the structure of the marketplace by virtue of being able to increase the potential patient popu-

lation to which this [stent] approach could be applied, and increasing the clinical effectiveness of the approach."

Moses says that one of the most important aspects of the treatment is that it has been shown to work for both low-risk and high-risk groups. "The percentage reduction of restenosis is fairly common across all groups," he says. "There is no question that this will have a huge impact in the field. This could be the platform for many endovascular technologies, as well as technologies that apply to other organs of the body. It may drive various developments in cardiovascular treatment, as well as other treatments such as oncology." Of particular interest will be the results of the SECURE trial, which is being conducted for patients who have no other recourse.

"The SECURE population is the worst-case scenario," says Costa, who is one of its investigators. "These patients have failed conventional treatments, angioplasty, bare-metal stenting, and bypass surgery. This is the only thing we can do for them. We expect that the technology will be effective, as it has been for all populations. The results may not be as positive for these patients, but they should be better than [those of] anything else they have available."

If drug-eluting stents can be shown to offer hope to patients who had almost none, that could spur even more advances as more firms realize the technology's potential. Drues says the technology is a major advance on the way to making cardiovascular treatment less invasive and more technology based.

"Stents open the artery and restore blood flow. Long term, keeping the artery open and preventing the disease from returning has to go beyond just simply a mechanical approach. Drug-eluting stents are that next step," he says. "Beyond that, we could see biologics-coated stents, which would involve gene therapy. Restenosis is actually a term that encompasses any of four completely different biological problems: atherosclerosis, hyperplasia, inflammation, and thrombosis. These are not one problem that can be completely solved with one solution. We may even see multiple drugs and genes being employed. The future of cardiovascular care will be combining devices, drugs, and biologics to take a more intelligent approach."

As J&J continues to make efforts to improve the reimbursement situation, so is it continuing to push for improvements to the product itself. For example, it is trying out a different metal that is more flexible but still as strong—enabling even more effective and precise drug delivery.

No road to progress is completely smooth, however. Cordis became aware of that when FDA received notice of 47 cases of stent thrombosis during the first months of Cypher's use in the United States. Rather than dismissing the problems as outliers or background noise (more than 50,000 patients received Cypher between launch and early July 2003), Cordis was quick to respond to them. On July 8, the company issued a letter to healthcare professionals reminding them of proper procedures. In particular, the letter asked doctors to make sure they have chosen the appropriate stent size, followed the proper patient-selection protocol, and used the correct antiplatelet regimen and the correct stent-deployment technique. FDA supported the company's actions.

"The problem seems concentrated at a few centers, and does not seem related to the device but to problems with operating technique," Firth says. "We and FDA are looking at it closely. Part of the problem may have been that we rolled out the smaller-size stent first and maybe some used it when the bigger size was necessary."

Implications for the Device Industry

Not only has the initial success of Cypher changed the way cardiovascular care is administered, it could be a harbinger of changes for the device industry as a whole.

"For a long time, device companies just took a mechanical approach to solving biological problems, but that may not make a lot of sense in the long run," Drues says. "The concern longer term is that when you get to the point of using a new drug or a gene, the requirements for the device world will change dramatically, in terms of the length of the development cycle and the number of patients that have to be tested. I don't know if the device companies fully appreciate what is involved. When factoring in medication and biology, problems are not as simple as they may seem if you're just looking at it [in terms of] engineering problem-solving skills."

Driscoll agrees, noting that "medical devices don't cure or eliminate disease. They deal effectively with particular symptoms. Of course, people want cures. Those will ultimately be produced by the biotech arena, unless the drug industry co-opts it. We are now on the road to devices and drugs working to provide treatments of symptoms, and eventually to combinations of devices, drugs, and biologics, and to all biotech. The ability for device-drug hybrids to increase effi-

2001

Cordis completes enrollment in SIRIUS, a large-scale, randomized U.S. clinical trial of the Cypher intended to evaluate its effect on in-stent restenosis.

Cordis reports results of RAVEL, a clinical trial involving 238 patients at 19 centers across Europe and Latin America. Six-month follow-up suggests the Cypher significantly reduces late lumen loss and reduces the incidence of restenosis to zero after placement in patients with coronary artery disease.

2002

Cordis receives CE Mark approval in Europe for the Cypher, making it the first approved drug-eluting stent and signaling a new era in the treatment of cardiovascular disease.

Cordis reports final results of its landmark SIRIUS study—the largest, most comprehensive study ever conducted to evaluate the performance of a new stent. Findings for 1058 patients at 53 U.S. treatment centers showed significantly less in-stent late lumen loss in patients with coronary artery disease treated with the Cypher.

CMS grants drug-eluting stent technology a code for incremental reimbursement.

2003

Cordis receives FDA approval to market the Cypher in the United States.

cacy of procedures is very significant. It is one step closer toward curing disease. They can produce a cure effectively by minimizing the long-term risk of disease recurring. The question is, the clinical results can look great, but do they hold up over time? Over the life of the patient? Or will there be unforeseen consequences of having the drug in the body? That has yet to be seen. Pharmacological science can be predicted but it is not as plain as devices. When you make changes to the biological system, repercussions flow through."

Another question is whether device companies that lack the in-house pharmaceutical and biotechnology expertise of J&J can muster the resources and commit the time to develop combination products properly.

"The barriers to entry are quite high," Firth says. "The R&D costs associated with combination products are high, because you have to evaluate drugs and polymers as well as devices." Given that, will the investment community provide any support for small and medium-sized companies that want to get into these areas, or will it remain the exclusive province of the big firms? That remains to be seen.

It also remains to be seen whether such time and expense can be justified when developing products for markets without the economic potential of cardiovascular care.

"The J&J model worked well in this instance, but it might not work so well if the drug maker were unwilling to license its product exclusively without more-direct involvement, if the market potential were smaller, or if the R&D for a potential product were expected to take much longer than the typical device life cycle," says Halasey.

No Room for Complacency

Drug-eluting stents will likely change the cardiovascular care market, as evidenced by the competing products likely to hit the U.S. market starting in 2004. Similarly, combination products will likely change the device industry, as evidenced by the top firms in the field looking at cross-industry partnerships. Given the talent and drive present in the device sector, the biggest innovation of one year won't stand the test of time if it is not followed by more breakthroughs and improvements. You can expect J&J won't rest on its laurels, nor will the rest of the industry. ■

Inter Partes Reexamination No. 95/001,102
Declaration of Campbell Rogers, M.D.
Exhibit 103

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TAXUS III Trial: In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation

Kengo Tanabe, Patrick W. Serruys, Eberhard Grube, Pieter C. Smits, Guido Selbach, Willem J. van der Giessen, Manfred Staberock, Pim de Feyter, Ralf Müller, Evelyn Regar, Muzaffer Degertekin, Jurgen M.R. Ligthart, Clemens Disco, Bianca Backx and Mary E. Russell

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TAXUS III Trial

In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation

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Background**—**The first clinical study of paclitaxel-eluting stent for de novo lesions showed promising results. We performed the TAXUS III trial to evaluate the feasibility and safety of paclitaxel-eluting stent for the treatment of in-stent restenosis (ISR).

Methods and Results**—**The TAXUS III trial was a single-arm, 2-center study that enrolled 28 patients with ISR meeting the criteria of lesion length ≤30 mm, 50% to 99% diameter stenosis, and vessel diameter 3.0 to 3.5 mm. They were treated with one or more TAXUS NIRx paclitaxel-eluting stents. Twenty-five patients completed the angiographic follow-up at 6 months, and 17 of these underwent intravascular ultrasound (IVUS) examination. No subacute stent thrombosis occurred up to 12 months, but there was one late chronic total occlusion, and additional 3 patients showed angiographic restenosis. The mean late loss was 0.54 mm, with neointimal hyperplasia volume of 20.3 mm^3. The major adverse cardiac event rate was 29% (8 patients; 1 non–Q-wave myocardial infarction, 1 coronary artery bypass grafting, and 6 target lesion revascularization [TLR]). Of the patients with TLR, 1 had restenosis in a bare stent implanted for edge dissection and 2 had restenosis in a gap between 2 paclitaxel-eluting stents. Two patients without angiographic restenosis underwent TLR as a result of the IVUS assessment at follow-up (1 incomplete apposition and 1 insufficient expansion of the stent).

Conclusions**—**Paclitaxel-eluting stent implantation is considered safe and potentially efficacious in the treatment of ISR. IVUS guidance to ensure good stent deployment with complete coverage of target lesion may reduce reintervention. **(*Circulation*. 2003;107:559-564.)**

Key Words: stents ■ restenosis ■ drugs

The development of coronary stents has revolutionized the field of interventional cardiology by reducing the incidence of restenosis after balloon angioplasty.[1,2] With the widespread clinical use of coronary stents, in-stent restenosis (ISR) has become the most challenging problem.[3] Previous pharmacological and mechanical approaches have shown disappointing results in eliminating this iatrogenic disease. Presently, intravascular brachytherapy is the only treatment for ISR proven to be effective in clinical randomized trials.[4–6] Brachytherapy requires special handling and is hampered by potential issues such as edge restenosis,[7,8] late thrombosis,[9] geographical miss,[10] late stent malapposition,[11] persisting dissection,[12,13] and positive vascular remodeling after treatment.[14,15]

Stent-based local drug delivery is expected to cause a revolutionary change in the field of percutaneous intervention, with recent clinical trials of paclitaxel or sirolimus-eluting stents demonstrating promising results in the treatment of de novo lesions.[16–19] Paclitaxel is a microtubule inhibitor presently used to treat several kinds of cancer, most commonly breast and ovarian. Microtubular dynamics regulate many of the inflammatory and profibrotic steps implicated in the restenotic cascade. This agent has been reported to reduce vascular cell proliferation and migration in vitro and in vivo.[20–23] In accordance with these experimental results, paclitaxel-eluting stents for de novo lesions showed no restenosis in the TAXUS I feasibility trial.[16] However, it has not been established whether this is applicable to a more complex patient group, such as patients with ISR. The TAXUS III trial is a single-arm, 2-center study aiming to evaluate the feasibility and safety of this eluting stent for the treatment of ISR.

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Methods

Patient Selection

Patients were eligible if they had ISR of a native coronary artery with objective evidence of ischemia. Angiographic inclusion criteria were lesion length ≤30 mm, 50% to 99% diameter stenosis, and vessel diameter between 3.0 and 3.5 mm. Patients were excluded if they had an acute myocardial infarction, left ventricular ejection fraction <30%, stroke within the last 6 months, a renal dysfunction (serum creatinine >1.7 μg/100 mL), or a contraindication to aspirin, clopidogrel, or ticlopidine. Between May 2001 and August 2001, patients were enrolled in two centers (Thoraxcenter, Rotterdam, the Netherlands, and Heart Center Siegburg, Siegburg, Germany). All patients gave written informed consent. The study was reviewed and approved by both institutions' ethics review committees.

Procedure

The stent used in the study was the TAXUS NIRx paclitaxel-eluting stent (Boston Scientific Corporation), with a total load of 1.0 μg/mm[2] of paclitaxel incorporated into a slow-release copolymer carrier system that gives biphasic release. The initial release is over the first 48 hours followed by slow release over the next 10 days. All stents were 15 mm long and 3.0 or 3.5 mm in diameter. Balloon predilatation was performed followed by NIRx paclitaxel-eluting stent implantation using conventional techniques. Postdilatation was performed if necessary. Periprocedural intravenous heparin was given to maintain an activated clotting time ≥250 seconds, and all patients received aspirin (at least 75 mg) and clopidogrel (300 mg loading dose followed by 75 mg once daily for 6 months).

Follow-Up

Clinical information was collected 6 and 12 months after procedure. Angiographic and intravascular ultrasound (IVUS) follow-ups were performed at the 6-month visit. Major adverse cardiac events (MACEs) were defined as death, myocardial infarction (MI), target-vessel repeat percutaneous coronary intervention, or coronary artery bypass grafting (CABG). MI was defined as Q-wave MI (development of new pathological Q waves in 2 or more leads with CK-MB levels elevated above normal) or non–Q-wave MI (elevation of CK levels to >2 times upper normal limit with CK-MB levels elevated above normal).

Angiographic Analysis

Coronary angiograms were obtained in multiple views after intracoronary nitrate. ISR was classified according to a modified Mehran classification.[3] Three coronary segments underwent quantitative angiography: in-stent, proximal edge, and distal edge segment. The in-stent analysis encompassed the entire length of all stents used during the procedure. The proximal and distal edge segments included up to 5 mm on either side of the in-stent segment. Quantitative coronary angiographic analysis was performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands).[24] The reference vessel diameter, minimal lumen diameter (MLD), and percent diameter stenosis were measured before procedure, after procedure, and at follow-up. Late loss was calculated as the difference between the MLD after procedure and that at follow-up. The target lesion was defined as the in-stent segment plus the proximal and distal edge segments. Angiographic restenosis was defined as >50% diameter stenosis within the target lesion.

IVUS Analysis

IVUS images were acquired after procedure and at 6-month follow-up using automated pull-back at 0.5 mm/s following intracoronary nitrate.[25] The total coronary analysis segment beginning 5 mm distal to and extending 5 mm proximal to the study stent was examined. A computer-based contour detection program was used for automated 3D reconstruction of the segments from up to 200 cross-sectional images. Lumen, stent boundaries, and external elastic membrane were detected using a minimum cost algorithm, and volumetric quantification was performed.[26,27] Percent volume obstruction was calculated as neointimal volume/stent volume×100. The quantitative ultrasound analysis was performed by the same independent core laboratory.

TABLE 1. Baseline Clinical Characteristics

Patients	28
Age, y	63.2±10.5
Male sex	19 (67.9)
Diabetes mellitus	4* (14.3)
Hypertension	18 (64.3)
Hypercholesterolemia	20 (71.4)
Family history	5 (17.9)
Current smoker	2 (7.1)
Unstable angina pectoris	2 (7.1)
Multivessel disease	7 (25)
Previous MI	16 (57.1)
Previous CABG	5 (17.9)

Values are presented as numbers (relative percentages) or mean±SD.
*In 1 patient, the information on diabetes mellitus was unknown.

Statistical Analysis

Continuous variables are expressed as mean±SD. Comparisons between postprocedure and 6-month follow-up measurements were performed with a 2-tailed paired t test. $P<0.05$ was considered statistically significant.

Results

Baseline Clinical and Lesion Characteristics

Twenty-eight patients with 28 target lesions were included. The patients' baseline clinical and lesion characteristics are summarized in Tables 1 and 2, respectively. The incidence of diabetes, previous MI, and previous CABG are in keeping with the higher risk population of ISR.[3] Diffuse ISR pattern

TABLE 2. Lesion Characteristics

No. of target lesions	28
Treated vessel	
Left anterior descending	10 (35.7)
Left circumflex	6 (21.4)
Right coronary artery	11 (39.3)
Left main	1 (3.6)
Type of ISR, Mehran classification	
IA, gap	0 (0)
IB, margin	3 (10.7)
IC, focal body	6 (21.4)
ID, multifocal	1 (3.6)
II, diffuse intrastent	13 (46.4)
III, proliferative	4 (14.3)
IV, total occlusion	1 (3.6)
Lesion length, mm	13.61±6.36
No. of implanted paclitaxel-eluting stents	
1 Stent per lesion	15 (53.6)
2 Stents per lesion	13 (46.4)

Values are presented as numbers (relative percentages) or mean±SD.

TABLE 3. Cumulative Clinical Outcome

	30 Days	6 Months	12 Months
Death	0	0	0
Q-wave MI	0	0	0
Non–Q-wave MI	1 (3.6)	1 (3.6)	1 (3.6)
CABG	0	1 (3.6)	1 (3.6)
Target vessel revascularization	0	6 (21.4)	6 (21.4)

Values are presented as numbers (relative percentages).

was present in 64% of target lesions. Thirteen lesions (46%) were treated with 2 paclitaxel-eluting stents.

Clinical Outcome

Table 3 summarizes MACE up to 12 months after procedure. No subacute stent thrombosis occurred, and no deaths were reported. There was 100% technical success in deploying the study stents; however, 1 patient had postprocedural non–Q-wave MI, yielding a 30-day MACE rate of 4%.

During the 6-month follow-up, an additional 7 patients had a MACE, for a 6-month rate of 29%. One patient underwent CABG attributable to progression of left main and ostial left circumflex lesions, which were at a distance from the target lesion. The remaining 6 patients underwent percutaneous target lesion revascularization (TLR). For 3 of these patients, the indication for TLR was angiographic restenosis. In the remaining 3 patients, 1 without angiographic restenosis had TLR because of anginal symptoms in the presence of a small MLD (1.33 mm). IVUS findings at follow-up triggered 2 additional interventions in the absence of angiographic restenosis. One showed incomplete stent apposition, the other showed insufficient stent expansion, and neither showed neointimal hyperplasia (percent volume obstruction, 0%). It was unknown whether the incomplete apposition was already present at baseline, because no IVUS assessment was performed after procedure. Between 6 and 12 months, no additional MACE was reported.

Angiographic and IVUS Outcome

Of 28 patients, 25 (89%) underwent 6-month follow-up angiography. Binary angiographic restenosis was documented in 4 patients (16%). One of these patients had target vessel total occlusion. Two paclitaxel-eluting stents had been implanted to treat ISR of a covered stent, which had been used to treat ISR of a gold-coated stent. Additional intervention was not undertaken, because the patient had no anginal symptoms.

Of the remaining 3 patients, 1 had restenosis in a bare metal stent implanted because of a dissection at the distal edge of the paclitaxel-eluting stent. Two patients had restenosis in a gap between 2 paclitaxel-eluting stents, as evident on IVUS (Figure 1). Minimal neointimal hyperplasia is seen in the segments with double contours of stent struts; however, where there is a single layer of stent struts, ie, a gap between the paclitaxel-eluting stents, occlusive neointimal tissue is evident. Hence, of the 4 with binary restenosis, 3 occurred within a region with no local delivery of paclitaxel.

The quantitative coronary angiographic data are summarized in Table 4. The mean reference vessel diameter was

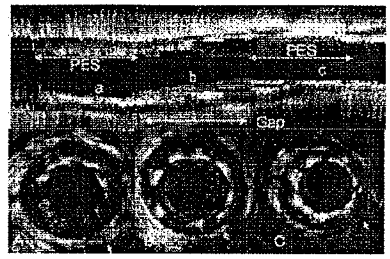

Figure 1. The IVUS images at follow-up of a patient who showed restenosis in a gap between the 2 paclitaxel-eluting stents (PES). Minimal neointimal hyperplasia was observed within the PES (A and C), whereas neointimal hyperplasia was noted in a gap (B). The cross-sectional views (A, B, and C) correspond to the a, b, and c sections of the longitudinal views.

2.75 mm. Figure 2 shows the cumulative distribution curve of MLD in the in-stent segment. The MLD at follow-up (1.84 mm) was significantly lower than that after procedure (2.40 mm). Diameter stenosis at follow-up was 30.8%, with an average in-stent late loss of 0.54 mm. Late loss of the proximal and distal edges were 0.20 and 0.11 mm, respectively, without angiographic restenosis.

Seventeen patients underwent IVUS examination at follow-up. The neointimal hyperplasia volume amounted to 20.3 ± 23.1 mm^3 with the stent volume of 172.1 ± 85.4 mm^3. In addition, serial analysis (n=14 pairs) of the total vessel volume after procedure (411.2 ± 332.9 mm^3) versus follow-up (435.8 ± 217.5 mm^3) showed no statistically significant change, suggesting that paclitaxel-eluting stent does not cause positive or negative vessel remodeling. No late acquired incomplete stent apposition was detected by serial IVUS investigation.

Subgroup Analysis

We performed subgroup analysis to estimate the treatment effect within stented segments directly exposed to local paclitaxel delivery by excluding the 3 patients who showed restenosis in a bare stent or a gap between 2 paclitaxel-eluting stents, as tabulated in Table 4. In this subgroup, the late loss and restenosis rate was 0.47 mm and 4.5%, respectively.

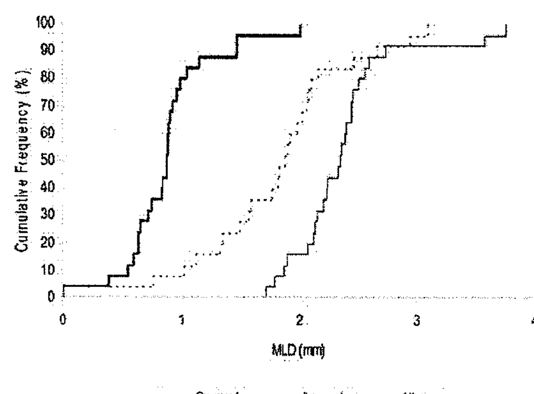

Figure 2. The cumulative distribution curve of the MLD.

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TABLE 4. QCA Data

	n	Proximal Edge, All Patients	In Stent, All Patients	Distal Edge, All Patients	n	In Stent, Subgroup*
Reference diameter						
Before procedure, mm	28	NA	2.75±1.20	NA	25	2.84±1.25
After procedure, mm	28	3.08±0.40	2.91±0.43	2.81±0.43	25	2.91±0.45
6-Month follow-up, mm	25	2.86±0.43†	2.67±0.42†	2.54±0.43†	22	2.64±0.45†
Minimal lumen diameter						
Before procedure, mm	28	NA	0.87±0.38	NA	25	0.90±0.39
After procedure, mm	28	2.67±0.54	2.40±0.44	2.27±0.47	25	2.41±0.46
6-Month follow-up, mm	25	2.45±0.54†	1.84±0.63†	2.17±0.49	22	1.93±0.61†
Percent diameter stenosis						
Before procedure, mm	28	NA	67.3±11.3	NA	25	67.1±11.8
After procedure, mm	28	13.9±9.4	17.4±7.6	19.3±11.0	25	16.9±7.6
6-Month follow-up, mm	25	14.3±10.5	30.8±20.5†	14.8±9.5	22	26.9±18.6†
Late loss, mm	25	0.20±0.40	0.54±0.51	0.11±0.33	22	0.47±0.48

*The subgroup is the group that excludes the patients who showed angiographic restenosis in a bare metal stent or a gap between the paclitaxel-eluting stents.

†$P<0.05$ vs after procedure.

Figure 3 shows the results of subgroup analysis between patients with single stent (n=13) and those with 2 stents (n=12). Post-hoc statistical analysis showed a significantly smaller MLD and larger diameter stenosis at follow-up for the 2-stent group ($P<0.01$). Post-hoc statistical analysis of IVUS data at follow-up reveal that percent volume obstruction in the single-stent group (n=10; length, 15.4±2.8 mm) was 12.4±15.7% for a stent volume of 111.9±27.9 mm^3, whereas percent volume obstruction in the 2-stent group (n=7, length 29.4±3.0 mm) was 10.1±8.2% for a stent volume of 258.1±60.3 mm^3. In this latter group, the analysis included only 1 of the 4 patients who had angiographic restenosis.

Discussion

In the present study, we report the first clinical experience with the TAXUS NIRx paclitaxel-eluting stent for the treatment of ISR. The major findings of the TAXUS III trial are as follows. First, this polymer-based paclitaxel-eluting stent is feasible and safe for the treatment of ISR with no subacute stent thrombosis. Second, late loss (0.54 mm) is seemingly diminished compared with historical controls. Third, angiographic restenosis rate is 16%; however, when present, it tends to occur in a gap between 2 paclitaxel-eluting stents. Fourth, the TLR rate of 21.4% (6 of 28 patients) is promising given that 3 were not performed according to predefined angiographic criteria.

Safety Consideration

At up to 12 months of clinical follow-up, there has been no late subacute stent thrombosis in our patient population, although clopidogrel was discontinued at 6 months. There was 1 patient with silent total occlusion who had preexisting in-stent restenosis in gold-coated and covered stent sandwich subsequently treated with the study stents. However, the mechanism of this occlusion is difficult to decipher, because the effect of paclitaxel on the adjacent covered stent sandwich is unknown and the covered stent precluded the IVUS assessment with respect to the detection of either a gap or an overlap. The promising safety data in our study contrasts with

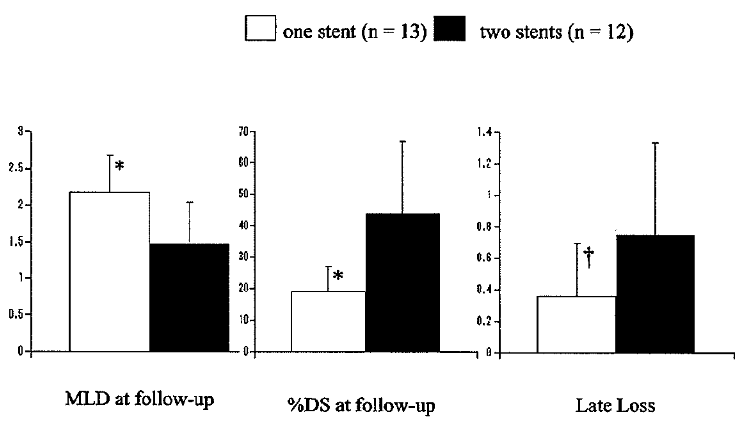

Figure 3. Post-hoc analysis between single stent and 2 stents of angiographic parameters (MLD at follow-up, percent diameter stenosis (DS) at follow-up, and late loss). It has to be emphasized that the 2 stent group include 1 total occlusion, 2 gaps between the stents, and 1 bare-stent restenosis. *$P<0.01$ vs 2 stents by unpaired *t* test; †$P=0.054$ versus 2 stents.

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the high incidence of late subacute stent thrombosis in the randomized Score trial, evaluating de novo lesions with the QuaDS stent that used 4 or 5 polymer sleeves to deliver high concentrations (800 μg/sleeve) of paclitaxel derivative.[28] The enrollment of the Score trial was prematurely stopped because of a major imbalance in MACE between the study and control groups associated with stent thrombosis. Previous animal studies showed that paclitaxel may delay the healing process in a dose-dependent manner,[29] and stent thrombosis is likely the result of incomplete healing and reendothelialization. Additional preclinical and clinical data will give insight as to whether the dose of paclitaxel (1.0 μg/mm^2 [loaded drug/stent surface area]) used in this trial will maintain the promising safety margin.

Efficacy of the TAXUS NIRx Paclitaxel-Eluting Stent for Treatment of In-Stent Restenosis

Previous reports using bare metal stent for treatment of ISR showed a late loss of 0.9 to 1.4 mm.[30–32] The overall late loss (0.54 mm) in our study was more favorable, even though it underestimates the treatment effect. If the 2 patients with restenosis attributable to a gap between 2 paclitaxel-eluting stents and the patient with restenosis in a bare stent are excluded, the adjusted late loss is 0.47 mm. In addition, the late loss in the single-stent group was 0.36 mm (Figure 3). These values are close to the loss of 0.35 mm (placebo group, 0.70 mm) observed in the TAXUS I trial on de novo coronary lesions treated with the same slow-release formulation. Furthermore, the neointimal volume from the TAXUS III patients with 1 NIRx stent was 15.6 mm^3, comparable to 14.8 mm^3 in the TAXUS I patients treated with one NIRx stent. These two values are both lower than the value of 21.6 mm^3 seen in the TAXUS I uncoated bare stent group. Taken together, these data suggest that paclitaxel on the NIRx seems to attenuate neointimal formation for ISR as well as de novo lesions.

Restenosis at the Gap

In 2 patients, IVUS identified a gap between 2 eluting stents that led to restenosis. Our hypothesis is that barotrauma from balloon inflation in an area of preexisting in-stent neointima may have triggered the local exuberant hyperplasia in the gap where the concentration of paclitaxel is insufficient to prevent neointimal hyperplasia. Accordingly, we speculate that paclitaxel does not diffuse substantially from the edge of the stent to have biological effect in the gap. Therefore, when treating ISR with the paclitaxel-eluting stents, covering the entire length of the previously implanted stents and providing a margin at either side may reduce TLR associated with restenosis near the drug-treated segments. With this in mind, IVUS guidance may be useful, and the advent of longer-eluting stents will be advantageous.

TLR Without Angiographic Restenosis

The TLR rate of this trial has been artificially inflated by reinterventions because of ultrasound or angiographic findings not always clinically driven or justified by predefined angiographic criteria. In this trial, 3 of 6 TLRs had diameter stenosis <50%. Two of these patients underwent TLR as a result of IVUS findings at follow-up. In one, there was an incomplete apposition at follow-up without postprocedural assessment. In the other patient, the stent was considered at follow-up to be insufficiently expanded, although the mean lumen area of the stent was 4.41 mm^2 without neointimal hyperplasia. The third patient had anginal symptoms despite a diameter stenosis of 32.5% and underwent TLR in an attempt to increase the MLD (1.33 mm) and reference diameter (1.96 mm). In this trial, the incidence of TLR may underestimate the clinical benefit related to the inhibition of neointimal hyperplasia resulting from the drug elution.

Study Limitations

The limitations of this study are its small sample size and single-arm open-label design without randomization. The angiographic follow-up rate was acceptable, although a higher IVUS follow-up rate may have provided more information on neointimal hyperplasia. Ongoing clinical follow-up will provide insight on long-term outcomes in this challenging population.

Conclusion

Paclitaxel-eluting stent implantation is considered safe and potentially efficacious in the treatment of ISR. The IVUS guidance to ensure good stent deployment with complete coverage of target lesion may reduce reintervention.

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TCT Daily: ZOMAXX I—Mixed Results with Zotarolimus-Eluting Stent

The ZoMaxx zotarolimus-eluting stent (Abbott Vascular Devices, Redwood City, CA) failed to achieve its noninferiority endpoint of in-segment late loss in a comparison with the paclitaxel-eluting Taxus stent, according to Bernard Chevalier, MD, of the Centre Cardiologie du Nord in St. Denis, France. The ZOMAXX I trial enrolled 401 patients, with 396 eligible for intent-to-treat analysis (199 patients randomized to ZoMaxx and 197 to Taxus).

In a late-breaking presentation, the median 9-month in-segment late loss was 0.29 mm with ZoMaxx (Abbott Vascular Devices) vs. 0.22 mm with Taxus (Boston Scientific, Natick, MA). The result exceeded the protocol-specified noninferiority margin of limit 0.25 mm by 0.02 mm, and therefore did not meet the primary endpoint.

Table 1. ZOMAXXI Secondary End Points.

	ZoMaxx	Taxus	P-value
In-stent restenosis (%)	12.9	5.7	0.03
In-stent late loss (mm)	0.67 ± 0.57	0.45 ± 0.48	>0.001
Neointimal volume obstruction (%)	14.6 ± 7.9	11.3 ± 9.6	0.02

In addition, the ZoMaxx stent demonstrated worse results according to several secondary parameters (Table 1).

Differences in target lesion revascularization and target vessel revascularization were not significant.

The ZoMaxx stent was highly deliverable, with 99% lesion and device success; there was no late-acquired incomplete stent apposition. The stent was shown to be safe, with a low overall rate of stent thrombosis (0.5%) and an absence of late stent thrombosis.

ZOMAXX I also showed that preclinical testing of drug-eluting stents cannot reliably predict human response. Zotarolimus is similar to sirolimus, with similar elution kinetics, but the stent showed significant differences in inhibition of neointimal proliferation.

Editorial

Living the Dream of No Restenosis

Paul S. Teirstein, MD

"If I am in a dream, please don't wake me" are the now-fabled words spoken by Patrick Serruys while viewing follow-up intravascular ultrasound images of sirolimus-eluting stents. The dream of an effective treatment for restenosis has eluded decades of effort by an army of investigators. Scores of devices, hundreds of drugs, and innumerable revascularization "strategies" have failed to eliminate the 10% to 50% risk of recurrence after angioplasty. The wasteland of failed anti-restenosis trials was expanded this summer by the 11 500-patient, hundred million dollar, mega-trial Prevention of REstenosis with Tranilast and its Outcomes (PRESTO), which demonstrated that tranilast (a cytokine inhibitor showing superb results in smaller pilot studies) was no better than placebo. When you take out a gallbladder, it doesn't grow back. Yet, no matter how much skill, experience, time, and effort the interventionist brings to the table, restenosis can entirely reverse a perfect procedural result within months. Until now, only the efficacy provided by vascular brachytherapy has offered hope to patients with in-stent restenosis.

See p 2007

In the present issue of *Circulation*, Sousa et al[1] provide a first glimpse at the 1-year data after the implantation of sirolimus-eluting stents. The report describes a very small, noncontrolled registry, yet the results are striking. After 12 months of follow-up in 30 patients and 6 months of follow-up in an additional 15 patients, the authors demonstrate a uniquely stable result. Using the highly sensitive technique of intravascular ultrasound, only a very minor proliferative response to injury was observed (<3% luminal volume obstruction). By angiography, the percent diameter stenosis increased only slightly from a mean of near 10% at the procedure's conclusion to ≈20% at 1 year. By the 12-month follow-up time point, not a single patient had sustained clinical or angiographic restenosis. These results are amplified by the recently reported, 238-patient, double-blind, randomized trial in Europe and Latin America, Randomized Double-Blind Study with the Sirolimus-Eluding BX Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Lesions (RAVEL), which found restenosis at 6 months was reduced from 26% in patients receiving placebo to 0 in those receiving sirolimus-eluting stents (P=<0.001). These dramatic results have created a stir in cardiology. Ever since angioplasty's inception, almost 25 years ago, restenosis has pulled on its reins, holding it back by denying patients a predictably long-lasting result. If the present data continue to be supported by ongoing, placebo-controlled, randomized trials (ie, Sirolimus-Coated BX Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Coronary Artery Lesions [SIRIUS] in the United States), our patients may finally receive the benefit of a minimally invasive revascularization technique that is also durable.

Of course, amid the fireworks, we should maintain our skepticism. The results are very preliminary, the number of patients studied small, the lesions enrolled simple, and the follow-up period still short. Indeed, one patient experienced a myocardial infarction at 14 months. The authors ascribe this to an "unstable plaque" proximal to the stent, but a pessimist might argue that sirolimus eluting from the adjacent stent may have weakened the fibrous cap that protects the underlying lipid pool. There is also a possibility that stent thrombosis, so crippling to early stenting and brachytherapy, could stymie the medicated stent model. Other toxicities may emerge, either from the medication itself or the polymer delivery vehicle. Preclinical trials of stents using different coatings and drugs have reported adverse reactions such as intimal hemorrhage, incomplete healing, intimal fibrin deposition, adventitial inflammation, and medial necrosis. These toxic effects could translate into clinical complications. Aneurysm, pseudoaneurysm, perforation, thrombosis, accelerated atherosclerosis, fibrosis, and systemic disorders are all potential adverse effects of drug-coated stent implants. The consequences for angioplasty patients are compelling because so many lives are involved. Worldwide, >1.5 million percutaneous coronary and peripheral angioplasty procedures are performed annually. Add our aging population and the kind of technological leap this study represents and that number could easily grow to >2 million. It is a bit intimidating to imagine that a serious late complication with an incidence of only 0.5% could affect >10 000 lives each year.

Drug-eluting stents may face other challenges. For example, longer-term follow-up may reveal results that are less permanent than anticipated. In fact, in the present study, if one looks critically at the minimal luminal diameter (MLD) changes over the 12-month follow-up period, subtle but noteworthy trends emerge. Two devices were evaluated, the "fast release" coated stents, wherein almost all drug was completely eluted by 15 days, and the "slow release" stent, which uses a polymer topcoat to slow drug release to 4 to 6 weeks. In fast release patients, the mean MLD was 2.67 mm

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Dr Teirstein is a consultant for and receives research grants from several manufacturers of products designed to reduce restenosis; he also receives royalties from the sale of radiation delivery catheters.

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immediately after implantation, virtually unchanged (2.69 mm) at 4 months, and then dropped to 2.32 mm (a 13.8% reduction) between 4 and 12 months. Interestingly, in the slow release group (the same formulation that is being tested in the randomized RAVEL and SIRUS trials), MLD changes occurred over a very different time course. The mean MLD was 2.74 mm immediately after implantation, dropped to 2.55 mm (a 7% reduction) 4 months later, and then dropped only slightly more (2.48 mm; another 2.8% decrease) between 4 and 12 months. Thus, the fast release group demonstrated better efficacy at 4 months, but by 12 months, MLD loss in the fast group had "caught up" to and surpassed that of the slow release group. One wonders if, over a longer follow-up period, an even slower releasing stent would maintain a larger lumen. These data, although subtle and involving small numbers of observations, underscore the need for further follow-up and further development before we fully understand the pharmacokinetics of stent-based drug delivery. One should remember that it was only after we obtained angiograms 3 years after catheter-based brachytherapy that small trends toward late "catch-up" were observed. Current plans for 18- and 24-month angiographic follow-up in this first group of sirolimus-stented patients will provide important long-term surveillance data.

As we stand on the verge of a "cure" for restenosis, it is interesting to ask, "Why has it taken so long?" Since the late 1970s, mammoth efforts and resources have been directed at restenosis. Today, optimism for drug-coated stents can be credited to the efforts of a very large number of researchers. Our understanding of restenosis evolved slowly. It was not until the early 1990s that several pivotal studies distinguished basic restenosis mechanisms such as early recoil, unfavorable remodeling, and the proliferative response to injury.[2,3] Other landmark studies established the concept that the extent of luminal "late loss" at follow-up is proportional to the amount of "acute gain" achieved during the initial procedure, which could be roughly described by the "late loss index."[4] These breakthroughs inspired an intense struggle to provide the largest possible initial lumen diameter under the banner "bigger is better." Although this approach provided incremental reductions in restenosis, today it is hard to imagine our naiveté in thinking we might eliminate restenosis using only mechanical devices like bare stents and atherectomy catheters.

Developing the stent as a drug delivery vehicle posed substantial challenges. The stent's stainless steel struts are poorly designed for drug delivery. Drugs do not bind readily to stent struts and, if bound, the surface area is not very large, providing only a limited drug reservoir. Thus, many researchers turned to stent coatings to facilitate the binding of drugs and to increase the available surface area. The initial stent coatings, however, were dismal failures.[5] In early animal trials, these polymers stimulated an intense inflammatory response, inciting more restenosis. Only recently have biocompatible materials such as methacrylates, polylactides, polyamides, chondroitins, gelatins, and hydrogels been developed that maintain adequate patency in the animal model. Many of these coatings were born of systematic trial-and-error experimentation involving multiple and lengthy animal implant studies. This required the development of predictable animal models of restenosis that allow detailed, quantitative documentation of the in vivo response to injury.[6] Another challenge was the difficult task of uniformly applying coatings to stent struts (typically accomplished by dipping) and then sterilizing the combination (usually with heat) without altering the properties of the coating or drug. Of course, a safe, biocompatible stent coating must be coupled with an efficacious drug. Manufacturers sprouted new divisions focused entirely on drug delivery to test scores of medications.

The story of sirolimus is illustrative. Rapamycin (the original name for sirolimus) was discovered in the mid 1970s by the microbiology program at Wyeth-Ayerst. Its antimicrobial activity, which was produced by *Streptomyces hygroscopicus*, was discovered in soil samples brought home by researchers from Easter Island (named on Easter Day, 1722, by Dutch explorers but better known as the Island of Rapa Nui by its Polynesian natives). Sirolimus development was soon abandoned, however, because its antifungal benefits were outweighed by its immunosuppressive toxicity. It was resuscitated years later in the late 1980s as a result of advances in transplant medicine. Suren Sehgal, at Wyeth-Ayerst, noted its structure and impact on T cells were similar to tacrolimus, a new T-cell inhibitor with 10 to 100 times more potency than cyclosporin. Investigation at Wyeth-Ayerst and several transplant centers eventually led to its Food and Drug Administration approval as a treatment for kidney transplant rejection. During these studies, transplant immunologists Randall Morris and Clare Gregory, at Stanford University, made the seminal observation that transplanted rat hearts treated with sirolimus had clean coronary arteries instead of the usual intimal thickening observed in allografts. Making a leap from transplant immunology to restenosis, they performed a series of experiments demonstrating reduced intimal proliferation in sirolimus-treated rats after carotid artery balloon injury.[7] Although allograft rejection and balloon angioplasty injured arteries by different mechanisms, both resulted in intimal proliferation that could be inhibited by sirolimus. Soon thereafter, Gallo et al[8], at The Mount Sinai School of Medicine (who had described many of its molecular mechanisms[9]), extended this observation, reporting a 52% reduction in intimal hyperplasia when sirolimus was delivered systemically in a porcine stent coronary restenosis model.

In 1996, as these early results emerged in the literature, a newly formed drug-device team at Johnson and Johnson's Cordis division, led by Robert Falotico and Gerard Llanos, was evaluating numerous drugs and coatings in parallel development programs. Of the many drugs tested, attention focused on sirolimus because the initial systemic trials demonstrated efficacy, the hurdles of incorporating the desired dose into a biocompatible polymer were overcome, and a collaboration with its owner, Wyeth-Ayerst, was successfully forged. This led to a series of implants by Suzuki et al[10] in the porcine model documenting a 51% reduction in intimal proliferation within sirolimus-coated compared with control stents. These results were replicated in rabbit and canine models and ultimately inspired the small, safety registry described in the present article. Surprisingly, the animal

experiments with sirolimus, while encouraging, did not foreshadow the near absence of intimal proliferation seen in the human trial reported by Sousa et al.[1] This observation highlights the differences between animal and human restenosis models. Today, we still do not have an animal model that accurately mimics the human condition, and the best model to test coated stents remains controversial.

In summary, the success of sirolimus required a collaboration between experts in both drug and device development, a great deal of empiric, trial-and-error experimentation with multiple drugs and polymers, good timing, and a little bit of luck sprinkled in.

The sirolimus story implies we have not seen the end of drug-coated stent development. Indeed, different medicated stents are currently in clinical trials, including paclitaxel, actinomycin-D, c-myc antisense, estradiol, and many others. Stent coatings have also grown more sophisticated. For example, one novel device uses drugs that are covalently bound to biodegradable "smart" polymers. As the polymer degrades, the drug is programmed to release over months to years. These "designer" coatings can release multiple drugs at different rates on different timelines. Other approaches include absorbent hydrogels applied to the stent surface that can "soak up" and then slowly release antiproliferative medications. Some plans even call on the physician to provide final assembly by dipping the hydrogel-coated stent (like fondue or sushi) into a drug-containing liquid just before deployment. The massive quantity of creative energy being applied to stent-based drug delivery can only improve on the promising results described by Sousa et al.[1]

Despite the early nature of this report and the admonition to remain skeptical, it is hard for many of us who have witnessed the growth of interventional cardiology to contain our enthusiasm. The sirolimus-eluting stent will likely be safe and extremely efficacious, and it will soon be joined by other successful drug-coated stents. Its impact on cardiology will probably be at least as important as the impact of stenting itself in the early 1990s. The end of restenosis could be the beginning of a new era in revascularization. The old aggressive, "bigger is better" technique will be replaced by a "kinder, gentler" approach achieving an adequate, but more stable lumen, with less procedural risk. Some of the classic "enemies" of percutaneous intervention, such as multivessel disease, diabetic patients, left main stenosis, small diameter vessels, long lesions, saphenous vein grafts, bifurcations, and femoral artery disease may well be conquered by drug-eluting stents, leaving chronic total occlusions as the major remaining challenge. Many patients now referred for bypass surgery will likely be candidates for a percutaneous approach. With a stent that doesn't renarrow, the threshold for intervention may be lowered. For example, as markers for vulnerable plaque are developed, one can envision non-restenosing stents being used to launch a preemptive strike against minimally stenotic, yet "at-risk" lesions. With their newly acquired ability to suppress intimal proliferation, stents themselves will proliferate.

Physicians and patients can be grateful for the important technological leaps in medicine represented by drug-coated stents. The excitement is well deserved, and our patients will be the beneficiaries. To some it may seem like a dream, but in reality, it just may be sweet dreams for restenosis.

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Key Words: Editorials ■ restenosis ■ stents ■ angioplasty ■ atherosclerosis

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Three-Year Clinical and Angiographic Follow-Up After Intracoronary Radiation : Results of a Randomized Clinical Trial

Paul S. Teirstein, Vincent Massullo, Shirish Jani, Jeffrey J. Popma, Robert J. Russo, Richard A. Schatz, Erminia M. Guarneri, Stephen Steuterman, Kathleen Sirkin, David A. Cloutier, Martin B. Leon and Prabhakar Tripuraneni

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Clinical Investigation and Reports

Three-Year Clinical and Angiographic Follow-Up After Intracoronary Radiation

Results of a Randomized Clinical Trial

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Background—Although several early trials indicate treatment of restenosis with radiation therapy is safe and effective, the long-term impact of this new technology has been questioned. The objective of this report is to document angiographic and clinical outcome 3 years after treatment of restenotic stented coronary arteries with catheter-based ^{192}Ir.

Methods and Results—A double-blind, randomized trial compared ^{192}Ir with placebo sources in patients with previous restenosis after coronary angioplasty. Over a 9-month period, 55 patients were enrolled; 26 were randomized to ^{192}Ir and 29 to placebo. At 3-year follow-up, target-lesion revascularization was significantly lower in the ^{192}Ir group (15.4% versus 48.3%; $P<0.01$). The dichotomous restenosis rate at 3-year follow-up was also significantly lower in ^{192}Ir patients (33% versus 64%; $P<0.05$). In a subgroup of patients with 3-year angiographic follow-up not subjected to target-lesion revascularization by the 6-month angiogram, the mean minimal luminal diameter between 6 months and 3 years decreased from 2.49 ± 0.81 to 2.12 ± 0.73 mm in ^{192}Ir patients but was unchanged in placebo patients.

Conclusions—The early clinical benefits observed after treatment of coronary restenosis with ^{192}Ir appear durable at late follow-up. Angiographic restenosis continues to be significantly reduced in ^{192}Ir-treated patients, but a small amount of late loss was observed between the 6-month and 3-year follow-up time points. No events occurred in the ^{192}Ir group to suggest major untoward effects of vascular radiotherapy. At 3-year follow-up, vascular radiotherapy continues to be a promising new treatment for restenosis. (*Circulation*. **2000;101:360-365.**)

Key Words: radioisotopes ■ radiotherapy ■ stents ■ coronary disease ■ restenosis

Restenosis continues to be the major limitation of catheter-based vascular procedures. Early preclinical studies have demonstrated radiation therapy to be a uniquely efficacious treatment for restenosis.[1-8] Although short-term clinical results have been promising, the long-term efficacy and, most importantly, safety of this technique are not known. The possibility of late adverse angiographic findings such as aneurysm formation, perforation, or accelerated vascular disease is of significant concern.[5-7] The objective of this report is to document angiographic and clinical outcome 3 years after treatment of restenotic stented coronary arteries with catheter-based ^{192}Ir.

Methods

The Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) trial was a double-blind, randomized trial comparing ^{192}Ir with placebo sources. The methods have been described previously.[9] This clinical trial was approved by the institution's human subjects and radiation safety committees. Patient inclusion criteria required a target lesion in a restenotic coronary artery that either already contained a stent or was a candidate for stent placement. If the lesion was not already stented, single or (if required) tandem coronary stenting (Johnson and Johnson Interventional Systems) was performed. If stents had been placed previously, redilation was undertaken, and often, additional stents were placed within the original stent to optimize the angiographic result. In all cases, high-pressure (>18 atm) balloon dilations were performed in an attempt to achieve a 0% residual stenosis within the stented segment. Patients were then randomly assigned to receive a 0.76-mm (0.03-inch) ribbon (Best Industries) containing sealed sources of either ^{192}Ir or placebo. The study ribbon was left in place for 20 to 45 minutes, as required to administer the prescribed dose of 800 to 3000 cGy to the adventitial border.[9]

See p 350

All patients were requested to return for repeat coronary angiography at 6 months and again at 3 years. Revascularization was repeated after

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follow-up angiography only if the patient had recurrent symptoms or if functional tests demonstrated the presence of coronary ischemia. At 3-year follow-up, patients were queried regarding any hospitalizations or procedures occurring since their index procedure. Medical records were obtained from each patient's primary treating physician along with copies of hospital records from all admissions and procedures. Where necessary, the county coroner's office was contacted to obtain data regarding the cause and date of patient deaths. Several patients who initially appeared lost to follow-up were located by a commercial service (1-800-US-SEARCH).

Core laboratory quantitative angiography was performed at the Brigham and Women's Hospital Center by individuals blinded to the treatment allocation, as previously described.[8,19] Selected serial cine frames, obtained from 2 unforeshortened projections and matched for position within the cardiac cycle with the use of side-by-side projectors, were digitized with a cine video converter, with the contrast-filled catheter used as the calibration standard. The reference vessel was defined as the vessel segment 5 mm proximal and distal to the radiation sources. Binary restenosis was defined as stenosis ≥50% of the luminal diameter of the stent and/or stent margin 5 mm proximal and distal to the radiation sources at follow-up. The assessment of binary restenosis at 3 years included only those patients with angiographic follow-up beyond 27 months, unless a target-lesion revascularization occurred earlier. Patients with restenosis at the 6-month angiogram but no target-lesion revascularization who lacked 3-year angiography (1 in each group) were excluded from the late binary restenosis analysis because stenosis regression could not be ruled out. An analysis of serial changes in minimal luminal diameter and diameter stenosis (Figures 4 and 5) included only those patients with 3-year angiograms who had not had a target-lesion revascularization by the 6-month angiogram.

Target-lesion revascularization was defined as coronary angioplasty or surgical bypass of the target vessel due to the presence of ≥50% diameter stenosis of the target lesion as measured by the core angiographic laboratory. The target lesion was defined as the stented segment in addition to the stent margins 5 mm proximal and distal to the radioactive or placebo sources. Thus, target-lesion revascularization included revascularization of both in-stent restenosis and restenosis at the stent or source margins due to "edge effect." Target-vessel revascularization included revascularization of the target lesion or a segment outside the target lesion but within the same vessel. Non-target-vessel revascularization was defined as revascularization of an epicardial vessel that did not contain the target lesion. Myocardial infarction was defined as an elevation of the MB fraction of creatinine kinase to a value 3 times the upper limit of the normal range.

For the analysis of continuous data, Mann-Whitney rank sum tests were used to assess differences between the 2 treatment groups, except for serial comparisons of luminal diameter and percent diameter stenosis, which were done with a 2-way ANOVA. The results are expressed as mean±SD. Categorical data were compared with the use of χ^2 or Fisher's exact test except for the composite clinical end point, which was analyzed by means of Kaplan-Meier survival analysis, with differences between the 2 treatment groups compared with the use of a Mantel-Cox test of significance.

Results

Between March 24 and December 22, 1995, 55 patients were enrolled in this study; 26 were randomized to ^{192}Ir and 29 to placebo. Baseline clinical and angiographic factors were similar in the 2 groups. In-stent restenosis was present in 62% of both treated and placebo groups (Table 1).

Clinical follow-up was obtained on or after the 3-year anniversary following the index procedure in 100% of living patients (Table 2). The mean time from index study procedure to clinical follow-up was similar in ^{192}Ir and placebo groups (39.1±2.3 versus 39.6±2.8 months; P=NS). Follow-up

TABLE 1. Baseline Clinical and Angiographic Characteristics of 55 Patients With Restenosis Assigned to Receive ^{192}Ir or Placebo

Characteristic	^{192}Ir Group (n=26)	Placebo Group (n=29)	P
Age, yr	69.3±9.7	68.8±10.8	NS
Male sex	73	76	NS
Elevated cholesterol level	54	59	NS
Diabetes mellitus	27	41	0.4
Unstable angina	42	55	NS
Previous myocardial infarction	38	34	NS
History of hypertension	65	69	NS
Previous restenoses			
No.	2.1±1.4	2.0±1.3	NS
>1	62	55	NS
>2	23	24	NS
In-stent restenosis	62	62	NS
No. of stents in target lesion			
1	38	45	NS
2	62	55	NS
Left ventricular ejection fraction, %	46.7±19.8	48.9±16.3	NS
Location of target lesion			
Saphenous vein graft	23	31	NS
Left anterior descending artery	31	38	NS
Ostial	31	41	NS
Aorto-ostial	12	17	NS
Lesion length, mm	12.89±7.05	11.86±6.77	NS
Lesion length ≥10 mm	58	45	NS

Plus-minus values are mean±SD. All other values are percentages of patients.

times ranged from 36 to 44 months in ^{192}Ir patients and 36 to 46 months in placebo patients.

At 3-year follow-up, target-lesion revascularization occurred in 4 patients (15.4%) in the ^{192}Ir group compared with 14 (48.3%) in the placebo group (P<0.01). One patient in each group sustained a new target-lesion revascularization after the 6-month follow-up angiogram: at 36 months for an asymptomatic ^{192}Ir patient and at 40 months for a symptomatic placebo patient (Figure 1). Both restenoses were focal and occurred within the target segment (not margins) at sites with <30% diameter stenosis on the 6-month angiogram. Target-vessel revascularization was also lower in ^{192}Ir patients, occurring in 8 (30.8%) treated versus 17 (58.7%) placebo patients (P=0.04). Target-vessel revascularization was higher than target-lesion revascularization in both groups because 4 patients in the treated group and 3 in the placebo group had revascularization of disease that was located at a significant distance (>5 mm) from the target lesion and believed therefore to be unrelated to edge effect. Two of these revascularization procedures in the treated group and 1 in the placebo group occurred between the 6-month and 3-year follow-up periods. Non-target-vessel revascularization, with or without target-vessel revascularization, was similar in both groups, occurring in 7 (26.9%) treated and 8 (27.6%) placebo

TABLE 2. Events at 3 Years

	^{192}Ir (n=26)	Placebo (n=29)	P
Clinical follow-up	100%	100%	NS
Time to follow-up, mo	39.1±2.3	39.6±2.8	NS
Range of follow-up, mo	36–44	36–46	
Death, %	3 (11.5)	3 (10.3)	NS
MI, %	1 (3.9)	3 (10.3)	NS
TLR, %	4 (15.4)	14 (48.3)	<0.01
TVR but no TLR, %	4 (15.4)	3 (10.3)	NS
TVR, %	8 (30.8)	17 (58.7)	0.04
Non-TVR but no TVR, %	4 (15.4)	4 (13.8)	NS
Non-TVR with TVR, %	3 (11.5)	4 (13.8)	NS
Non-TVR, %	7 (26.9)	8 (27.6)	NS
Revascularization but no TLR	8 (30.8)	7 (24.1)	NS
Any revascularization	12 (46.2)	21 (72.4)	<0.05
Death, MI, or TLR, %	6 (23.1)	16 (55.2)	0.01
Death, MI, or TVR, %	10 (38.5)	19 (65.5)	<0.05
Death, MI, or any revascularization, %	13 (50)	23 (79.3)	0.02
Restenosis,* %	7 (33.3%) (n=21)	14 (63.6%) (n=22)	<0.05

MI indicates myocardial infarction; TLR, target-lesion revascularization; and TVR, target-vessel revascularization.

Numbers are not mutually exclusive.

*≥50% diameter stenosis of the stent or stent border.

patients. In both groups, revascularization of nontarget lesions over the follow-up period was common. Eight (30.8%) treated and 7 (24.1%) placebo patients who did not need target-lesion revascularization did require revascularization of other, nontarget lesions. Thus, by 3 years, a total of 12 (46.2%) treated and 21 (72.4%) placebo patients had undergone subsequent revascularization procedures (Table 2).

There were 3 deaths in each group. Two of the deaths in the placebo group were cardiac deaths (at 8 and 11 months) associated with myocardial infarction, and the third (at 30 months) occurred in the postoperative period after bypass surgery for a target-lesion restenosis. One death in the ^{192}Ir group (at 23 months) occurred in the postoperative period

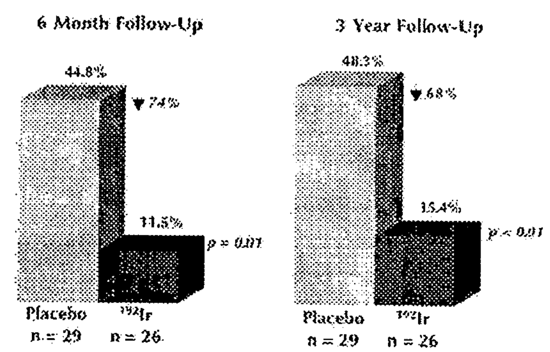

Figure 1. Rate of target-lesion revascularization in ^{192}Ir versus placebo patients at 6-month and 3-year follow-up. One patient in each group sustained a new target-lesion revascularization between the 6-month and 3-year time points. Clinical efficacy observed at 6 months is maintained at 3-year follow-up.

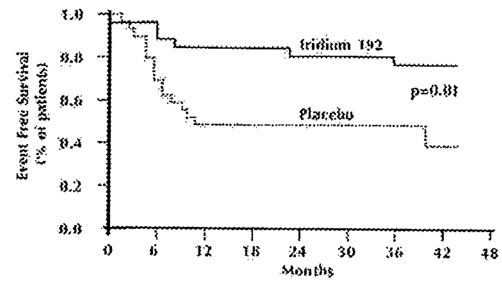

Figure 2. Kaplan-Meier curves for event-free survival in ^{192}Ir and placebo groups. Event-free survival was defined as survival without myocardial infarction or repeated revascularization of target lesion. Curves diverge at 3 months, and difference increases over next 7 months, after which clinical events are infrequent.

after bypass surgery for a non–target-lesion stenosis. Another death in the ^{192}Ir group occurred in a patient who had self-terminated ticlopidine on day 3 and sustained a stent thrombosis that resulted in acute myocardial infarction on day 18 after the index procedure. Angiography during the acute thrombotic event and again at 6-month follow-up demonstrated 100% occlusion of the target lesion. This patient died 18 months after the study procedure of complications of abdominal surgery for diverticulitis. The third death was sudden (at 39 months) in a ^{192}Ir-treatment-failure patient who had a target-lesion revascularization at 8 months.

The composite end point of death, myocardial infarction, or target-lesion revascularization was significantly lower in ^{192}Ir versus placebo patients (23.1% versus 55.2%; $P=0.01$). Life-table analysis of this composite end point is displayed in Figure 2. Differences in clinical events were driven largely by differences in the need for target-lesion revascularization and become apparent at ≈3 months. The 2 curves continue to diverge until 10 months, after which clinical events are infrequent. However, owing to the large number of non–target-lesion revascularizations, differences in the composite end point of death, myocardial infarction, and target-vessel revascularization (38.5% versus 65.5%; $P<0.05$) and differences in death, myocardial infarction, and any revascularization (50% versus 79.3%; $P=0.02$) were less pronounced.

As previously reported, initial follow-up angiography was obtained at a mean of 6.7 months in 96.4% of patients.[5] At the 6-month time point, restenosis rates were significantly reduced in the ^{192}Ir group (17% versus 54%; $P=0.01$). For the present report, all patients were asked to return for a repeat angiogram at 36 months. The mean interval from index procedure to late follow-up angiography was 36.7±4.5 months in ^{192}Ir patients compared with 39.1±2.6 months in placebo patients ($P=0.05$). This late angiogram was obtained in 19 (73.1%) of ^{192}Ir and 18 (62.1%) of placebo patients ($P=$NS). This represents 82.6% of living ^{192}Ir and 69.2% of living placebo patients ($P=$NS). None of the 4 living ^{192}Ir and 8 living placebo patients who refused 3-year angiography had symptoms of angina. Each of these patients had undergone numerous catheterization procedures in the past, had now broken the cycle of repeated invasive procedures, and adamantly refused catheterization.

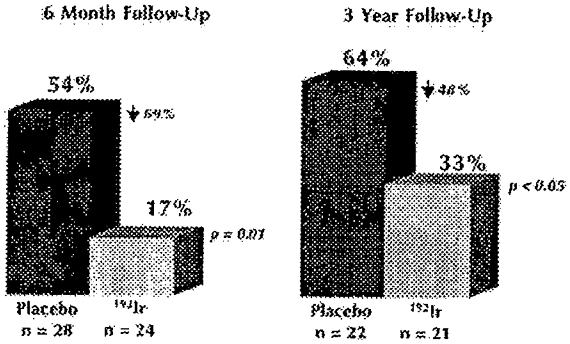

Figure 3. Rate of angiographic restenosis (≥50% diameter stenosis of stent and/or stent margin) in ^{192}Ir versus placebo patients at 6-month and 3-year follow-up. Assessment of restenosis at 3 years included only those patients with angiographic follow-up beyond 27 months unless a target-lesion revascularization occurred earlier. Whereas restenosis rates were reduced by 69% on 6-month angiogram, restenosis was only reduced by 48% by 3-year angiogram. However, at 3 years, this reduction in restenosis was significant ($P<0.05$).

At the 3-year follow-up, angiographic restenosis (≥50% stenosis of the luminal diameter) either within the stent or at its border (outside the stent but spanned by the study ribbon) was observed in 33.3% of ^{192}Ir patients compared with 63.6% of placebo patients ($P<0.05$). Thus, whereas restenosis rates were reduced by 69% by the 6-month angiogram, restenosis was only reduced by 48% by the 3-year angiogram. However, at 3 years, this reduction in restenosis was still significant ($P<0.05$) (Figure 3).

To better characterize the late natural history after radiation therapy, angiograms were analyzed in patients who were alive and had not had a target-lesion revascularization by the 6-month angiographic time point. This is an important subgroup of patients, because these lesions were not subjected to interim interventions, and therefore, they best represent the late natural history after radiation therapy. Late follow-up

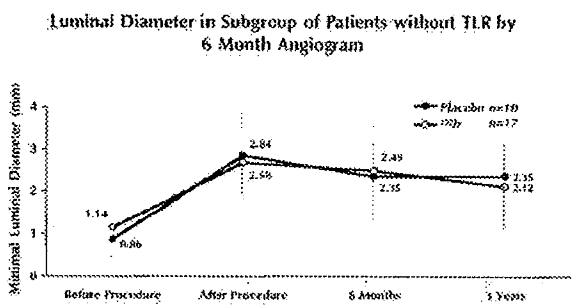

Figure 4. Serial changes in mean±SD minimal luminal diameter in selected patients over study period. Only patients with 3-year angiographic follow-up who did not have target-vessel revascularization by 6-month angiogram are included. A small reduction in mean minimal luminal diameter was observed between 6 months and 3 years in ^{192}Ir patients that was not found in the placebo group. TLR indicates target-lesion revascularization. For ^{192}Ir patients: after procedure vs 6 months, $P=0.30$; after procedure vs 3 years, $P<0.01$; 6 months vs 3 years, $P=0.15$. For placebo patients: after procedure versus 6 months, $P=0.01$; after procedure versus 3 years, $P=0.12$; 6 months versus 3 years, $P=0.98$.

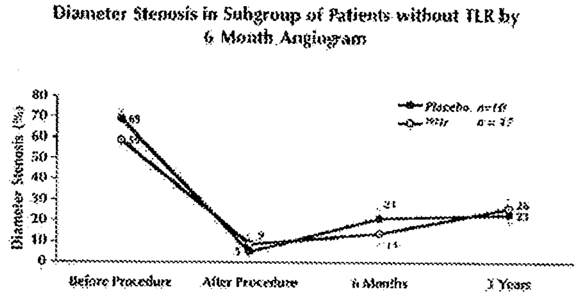

Figure 5. Serial changes in mean±SD percent diameter stenosis in selected patients over study period. Only patients with 3-year angiographic follow-up who did not have target-vessel revascularization by 6-month angiogram are included. A small increase in diameter stenosis was observed between 6 months and 3 years in the ^{192}Ir group that was not matched by the placebo group. TLR indicates target-lesion revascularization. For ^{192}Ir patients: after procedure vs 6 months, $P=0.36$; after procedure vs 3 years, $P=0.05$; 6 months vs 3 years, $P=0.25$. For placebo patients: after procedure vs 6 months, $P=0.02$; after procedure vs 3 years, $P=0.08$; 6 months vs 3 years, $P=0.75$.

angiography was obtained in 17 (81%) of 21 eligible ^{192}Ir and 10 (71.4%) of 14 eligible placebo patients in this subgroup. The mean minimal luminal diameter between the 6-month and 3-year angiograms decreased from 2.49±0.81 to 2.12±0.73 mm ($P=0.15$) in ^{192}Ir patients but was unchanged in placebo patients in this subgroup (Figure 4). Thus, when the analysis was confined only to lesions that were "untouched by human hands" by the 6-month angiogram, a small reduction in minimal luminal diameter was observed between 6 months and 3 years in the treated group that was not found in the placebo group. Correspondingly, there was a small amount of late "catch up" in percent diameter stenosis between 6 months and 3 years in ^{192}Ir-treated patients that was not matched by the placebo group. The percent diameter stenosis increased from 14±28% at 6 months to 26±28% ($P=0.25$) at 3 years in ^{192}Ir-treated patients but only increased from 21±24% to 23±17% ($P=0.75$) in placebo patients (Figure 5).

Although our sample size was small, it is notable that only 24% of treated and 20% of placebo patients had a reduction in diameter stenosis of >15% between the 6-month and 3-year angiograms. Thus, most late serial changes in percent diameter stenosis were small. However, between the 6-month and 3-year angiograms, 4 patients in the treated group had an increase in diameter stenosis that brought the final luminal diameter to >50%, whereas only 1 patient in the placebo group crossed this 50% threshold. Of the 3 patients in the treated group who crossed over the 50% threshold but did not have a target-lesion revascularization, the absolute increases in diameter stenosis were small (14%, 15%, and 35%); however, this small amount of late catch up in the treated group did narrow the difference in dichotomous restenosis rates between the 2 groups. No aneurysms, pseudoaneurysms, or perforations were observed by the core angiographic laboratory on any follow-up angiograms of either the ^{192}Ir group or the placebo group.

Discussion

After 3 years of clinical and angiographic follow-up, treatment with ^{192}Ir continues to demonstrate improved clinical

outcome compared with placebo. With 100% clinical follow-up and each living patient followed up for ≥36 months, the clinical benefits initially observed at 6 and 24 months[9,11] were maintained, and no unexpected, radiation-related adverse events were identified. Interestingly, in ^{192}Ir-treated patients, there were no clinically apparent restenoses after the initial follow-up angiogram until protocol-mandated 3-year angiography documented a high-grade target-lesion restenosis in an asymptomatic treated patient. This lesion was located in the proximal segment of a large-diameter left anterior descending artery. Although the patient was asymptomatic, noninvasive testing (performed after the follow-up diagnostic angiogram) did demonstrate silent coronary ischemia, which prompted a return to the catheterization laboratory for repeat angioplasty. There was 1 late target-lesion revascularization after the 6-month angiogram in the placebo group. This patient, who initially resisted 3-year angiography, underwent restudy owing to recurrence of symptoms at 40 months, was found to have significant proximal right coronary artery stenosis, and underwent repeat angioplasty.

Over the 3-year follow-up period, the composite clinical event rate (death, myocardial infarction, or target-lesion revascularization) in the treated group was lower than in the placebo group (23.1% versus 55.2%; $P=0.01$). The 3 deaths in the ^{192}Ir group had clearly identified causes: 1 was a consequence of elective bypass surgery of a nontarget lesion, another was a sudden death in a treatment-failure patient, and another was due to complications following abdominal surgery 18 months after a stent thrombosis. Although it is possible that the stent thrombosis was related to radiation exposure (in the absence of ticlopidine), this vessel was documented to be 100% occluded on angiography 6 months after the index procedure and was therefore unlikely to be a site of sudden coronary closure, perforation, or other acute cardiac event.

Another important finding of the present study was the large number of non-target-lesion revascularization procedures in both the treated and placebo groups over the 3-year follow-up period. Fully 30.7% of treated and 24.1% of placebo patients who did not need target-lesion revascularization did require revascularization of other nontarget lesions (Table 2). Thus, by the end of the follow-up period, 50% of treated patients and 79.3% of placebo patients had sustained a clinical event. It should be emphasized, therefore, that although γ-radiation effectively reduced events associated with the target lesion, this local therapy did not affect the development of disease outside of the target segment. Late events were common, even in treated patients.

At 3 years, the angiographic restenosis rate in the treated group was 48% lower than in the placebo group (33% versus 64%; $P<0.05$). In ^{192}Ir patients who did not undergo target-lesion revascularization by the 6-month follow-up angiogram, the mean minimal luminal diameter decreased and the mean percent diameter stenosis increased by a small amount between the 6-month and 3-year angiograms. This reduction in diameter was not matched by the placebo group, whose mean minimal luminal diameter was unchanged over the late follow-up period. The number of patients with serial angiographic measurements was small, and standard deviations were large, and therefore, the possibility exists that the play of chance alone may account for these observations. Nevertheless, our findings may contradict the concept that radiation, in a stented artery, "freezes" the postprocedure angiographic result. The response of the vessel to radiation appeared to be somewhat dynamic over the 3-year follow-up period, and in some patients, there was continued late loss. This late loss was small, but in 4 treated patients, it was enough to cross the 50% diameter threshold, provoking an increase in the dichotomous restenosis rate. Although the increase in restenosis rate in treated patients from 17% to 33% over the 3-year period raises some concerns about the prognosis for an even longer follow-up period, it should be emphasized that all 4 patients were asymptomatic, and only 1 patient had a high-grade stenosis with evidence of ischemia that prompted revascularization. Also, this initial pilot trial intentionally prescribed a relatively low dose of radiation; higher radiation exposures may further improve long-term results. Importantly, late angiographic follow-up in the present study revealed no evidence of perforation, aneurysm, or pseudoaneurysm in ^{192}Ir-treated patients. Thus, no safety issues unique to radiotherapy have been identified.

Our late results differ from the reported long-term follow-up after stent implantation for de novo disease. In the only published study examining 3-year angiographic outcome after initial stent implantation (without radiation),[12] the minimal luminal diameter increased slightly but significantly between the 6-month and 3-year angiograms. Several other clinical trials using vascular radiotherapy have been published.[13-17] In 1 study, 7-year follow-up documented high patency rates after femoropopliteal arteries undergoing angioplasty were exposed to intravascular γ-radiation.[14-16] Other reports evaluating the long-term effects of coronary radiation are pending.[13]

Study Limitations

The most important limitation of this study is its small sample size. The distribution of baseline characteristics was not entirely even, with a trend toward more diabetic patients in the placebo group. Also, more asymptomatic patients in the placebo group refused 3-year angiography, which may have increased the restenosis rate documented in the placebo arm.

Conclusions

With 100% clinical follow-up 3 years after study entry, the clinical efficacy of ^{192}Ir appears durable. In ^{192}Ir-treated patients, target-lesion revascularization was reduced by 74% at 6 months and 68% at 3 years. Angiographic restenosis was reduced by 69% at 6 months but only 48% at 3 years because of small reductions in luminal diameter over the longer follow-up period. No perforations, aneurysms, pseudoaneurysms, or other safety issues were observed. At the 3-year time point, vascular radiotherapy continues to be a promising treatment for restenosis.

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